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CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

65. Alumina Catalysts for Vapour-phase Organic Dehydrations, Deaminations, etc.
By G. FEACHEM and H. T. S. SWALLOW 267

79. The Periodic System of the Chemical Elements in Three Dimensions. (The "Five–Five System.")
By A. G. OPPEGAARD 318

80. The Structure of Certain Polysulphides and Sulphonyl Sulphides. Part I. A Preliminary *X*-Ray Survey.
By I. M. DAWSON, A. McL. MATHIESON, and J. MONTEATH ROBERTSON . . 322

81. The Correlation of Vibrational Absorption Spectra with Molecular Structure.
By H. W. THOMPSON 328

82. Bond Energies in Peroxides, and the Energy evolved in the Reaction $H + O_2 = HO_2$.
By A. D. WALSH 331

90. Acid–Base Catalysis in Non-aqueous Solvents. Part XI. The Halogenation of Acetone by Various *N*-Halogen Compounds in Chlorobenzene Solution at 50°.
By R. P. BELL and A. D. S. TANTRAM 370

93. A Contribution to the Chemistry of the Inner Complex Salts of Dimethylglyoxime.
By FRITZ FEIGL and HANS A. SUTER 378

Organic.

61. Constituents of "*Cortex Piscidiæ Erythrinæ*". Part I. The Structure of Piscidic Acid.
By WALTER BRIDGE, FREDERICK COLEMAN, and ALEXANDER ROBERTSON . . 257

62. Attempts to find New Chemotherapeutic Amidines. Part IX. Derivatives of 1 : 1-Diphenylethylene and Naphthalene.
By J. N. ASHLEY, J. F. GROVE, and T. HENSHALL 261

63. The Preparation of Symmetrical Dinitrodiphenyls by the Ullmann Reaction
By W. DAVEY and R. W. LATTER 264

64. Curare Alkaloids. Part VII. Constitution of *dextro*Tubocurarine Chloride.
By HAROLD KING 265

66. Halogenated Ketones. Part I. The Bromination of Acetone and Methyl Ethyl Ketone.
By J. R. CATCH, D. F. ELLIOTT, D. H. HEY, and E. R. H. JONES . . . 272

67. Halogenated Ketones. Part II. The Bromination of Methyl Propyl and Methyl *iso*Propyl Ketone.
By J. R. CATCH, D. H. HEY, E. R. H. JONES, and WALTER WILSON . . . 276

68. Halogenated Ketones. Part III. The Preparation of Bromomethyl Ketones by the Diazomethane Reaction.
By J. R. CATCH, D. F. ELLIOTT, D. H. HEY, and E. R. H. JONES . . . 278

69. Halogenated Ketones. Part IV. The Application of the Friedel–Crafts Reaction to the Preparation of Halogenated Aliphatic Ketones.
By J. R. CATCH, D. F. ELLIOTT, D. H. HEY, and E. R. H. JONES . . . 278

70. A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXIII. Phthalazine Derivatives from 4′-Nitro-2′ : 5′-dimethoxybenzene-2-naphthol-1-diazosulphonate.
By (the late) F. M. ROWE, R. L. DESAI, and A. T. PETERS 281

71. Reactions of Unsaturated Compounds. Part V. The Action of Organic Peracids on β-Di*iso*butylene (2 : 4 : 4-Trimethylpent-2-ene).
By A. BYERS and W. J. HICKINBOTTOM 284

72. A Study of the Properties of Fluorine-substituted 5-Aminoacridines and Related Compounds. Part III. Some 5-Amino-1 : 2 : 2′ : 3′-Pyridoacridines.
By J. H. WILKINSON and I. L. FINAR 288

PAGE

73. Derivatives of Arsacridine. Part I.
By C. L. HEWETT, L. J. LERMIT, H. T. OPENSHAW, A. R. TODD, A. H. WILLIAMS, and F. N. WOODWARD 292

74. Derivatives of Arsacridine. Part II.
By R. E. DAVIES, H. T. OPENSHAW, F. S. SPRING, R. H. STANLEY, and A. R. TODD 295

75. Anhydrides of Polyhydric Alcohols. Part X. The Conversion of Glucamine into 1 : 4-Anhydrosorbitol. The Constitution of Benzylidene 1 : 4-Anhydrosorbitol.
By V. G. BASHFORD and L. F. WIGGINS 299

76. Amidines. Part VIII. Preparation of Amidines from Cyanides, Ammonia or an Amine, and an Ammonium or Substituted-ammonium Salt.
By P. OXLEY, M. W. PARTRIDGE, and W. F. SHORT 303

77. Esters of 1-Hydroxy-2-naphthoic Acid, and Naphthol-blue Dyes therefrom.
By M. PIANKA and H. C. BARANY 309

78. A New Synthesis of DL-Threonine.
By J. ATTENBURROW, D. F. ELLIOTT, and G. F. PENNY 310

83. Interactions between Non-bonded Atoms, and the Structure of *cis*-Decalin.
By D. H. R. BARTON 340

84. The Mechanism of Oxidation of Monoethenoid Fatty Acids and Esters. The Course of Thermal Catalytic Oxidation of Methyl Oleate.
By J. H. SKELLON 343

85. The Decomposition Reactions of the Aromatic Diazo-compounds in Aqueous Solution explained on Simple Electronic Theory, and without Recourse to the Current Free-radical Hypothesis.
By HERBERT H. HODGSON 348

86. Cinnolines. Part XVI. 4-Hydroxy-3-methylcinnolines.
By J. R. KENEFORD and J. C. E. SIMPSON 354

87. Cinnolines. Part XVII. A Simple Method for the Preparation of 4-Aminocinnolines.
By J. R. KENEFORD, K. SCHOFIELD, and J. C. E. SIMPSON 358

88. The Chemistry of Simple Heterocyclic Systems. Part I. Reactions of 6- and 7-Nitro-4-hydroxyquinazoline and their Derivatives.
By J. S. MORLEY and J. C. E. SIMPSON 360

89. Halogenation of *m*-5- and *m*-2-Xylenols. Preparation and Structure of Certain Polyhalogeno-*m*-5- and -*m*-2-xylenols.
By C. H. R. ELSTON, A. T. PETERS, and (the late) F. M. ROWE 367

91. *p*-(2-Chloroethylthio)phenyldichloroarsine.
By H. T. OPENSHAW and A. R. TODD 374

92. Azlactones and Phenylacetic Acids derived from the 2-Nitro-derivatives of Vanillin, *iso*Vanillin, and Veratraldehyde.
By S. F. MACDONALD 376

NOTES—Preparation of Some *p*-Alkylsulphonylbenzylammonium Chlorides.
By J. CYMERMAN, A. KOEBNER, and W. F. SHORT 381

A Synthesis of Leptospermone.
By L. H. BRIGGS, C. H. HASSALL, and W. I. TAYLOR 383

The Preparation of *o*-Nitroacetophenone.
By K. SCHOFIELD and T. SWAIN 384

The Interaction of Tetra-arylglycols and Pyridinium Salts.
By ALEXANDER SCHÖNBERG and AHMED MUSTAFA 385

THE PEDLER LECTURE. Recent Developments in the Vitamin A Field.
By SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S. 386

OBITUARY NOTICES 394

INDEX OF AUTHORS' NAMES.

Ashley, J. N., Grove, J. F., and Henshall, T., 261.
Attenburrow, J., Elliott, D. F., and Penny, G. F., 310.
Barany, H. C. See Pianka, M.
Barton, D. H. R., 340.
Bashford, V. G., and Wiggins, L. F., 299.
Bell, R. P., and Tantram, A. D. S., 370.
Bridge, W., Coleman, F., and Robertson, A., 257.
Briggs, L. H., Hassall, C. H., and Taylor, W. I., 383.
Byers, A., and Hickinbottom, W. J., 284.
Catch, J. R., Elliott, D. F., Hey, D. H., and Jones, E. R. H., 272, 278.
Catch, J. R., Hey, D. H., Jones, E. R. H., and Wilson, W., 276.
Coleman, F. See Bridge, W.
Cymerman, J., Koebner, A., and Short, W. F., 381.
Davey, W., and Latter, R. W., 264.
Davies, R. E., Openshaw, H. T., Spring, F. S., Stanley, R. H., and Todd, A. R., 295.
Dawson, I. M., Mathieson, A. McL., and Robertson, J. M., 322.
Desai, R. L. See Rowe, F. M.
Elliott, D. F. See Attenburrow, J., and Catch, J. R.
Elston, C. H. R., Peters, A. T., and Rowe, F. M., 367.
Feachem, G., and Swallow, H. T. S., 267.
Feigl, F., and Suter, H. A., 378.
Finar, I. L. See Wilkinson, J. H.
Grove, J. F. See Ashley, J. N.
Hassall, C. H. See Briggs, L. H.
Heilbron, Sir I., 386.
Henshall, T. See Ashley, J. N.
Hewett, C. L., Lermit, L. J., Openshaw, H. T., Todd, A. R., Williams, A. H., and Woodward, F. N., 292.
Hey, D. H. See Catch, J. R.
Hickinbottom, W. J. See Byers, A.
Hodgson, H. H., 348.
Jones, E. R. H. See Catch, J. R.
Keneford, J. R., Schofield, K., and Simpson, J. C. E., 358.
Keneford, J. R., and Simpson, J. C. E., 354.
King, H., 265.
Koebner, A. See Cymerman, J.
Latter, R. W. See Davey, W.
Lermit, L. J. See Hewett, C. L.
MacDonald, S. F., 376.
Mathieson, A. McL. See Dawson, I. M.
Morley, J. S., and Simpson, J. C. E., 360.
Mustafa, A. See Schönberg, A.
Openshaw, H. T., and Todd, A. R., 374.
Openshaw, H. T. See also Davies, R. E., and Hewett, C. L.
Oppegaard, A. G., 318.
Oxley, P., Partridge, M. W., and Short, W. F., 303.
Partridge, M. W. See Oxley, P.
Penny, G. F. See Attenburrow, J.
Peters, A. T. See Elston, C. H. R., and Rowe, F. M.
Pianka, M., and Barany, H. C., 309.
Robertson, A. See Bridge, W.
Robertson, J. M. See Dawson, I. M.
Rowe, F. M., Desai, R. L., and Peters, A. T., 281.
Rowe, F. M. See also Elston, C. H. R.
Schönberg, A., and Mustafa, A., 385.
Schofield, K., and Swain, T., 384.
Schofield, K. See also Keneford, J. R.
Short, W. F. See Cymerman, J., and Oxley, P.
Simpson, J. C. E. See Keneford, J. R., and Morley, J. S.
Skellon, J. H., 343.
Spring, F. S. See Davies, R. E.
Stanley, R. H. See Davies, R. E.
Suter, H. A. See Feigl, F.
Swain, T. See Schofield, K.
Swallow, H. T. S. See Feachem, G.
Tantram, A. D. S. See Bell, R. P.
Taylor, W. I. See Briggs, L. H.
Thompson, H. W., 328.
Todd, A. R. See Davies, R. E., Hewett, C. L., and Openshaw, H. G.
Walsh, A. D., 331.
Wiggins, L. F. See Bashford, V. G.
Wilkinson, J. H., and Finar, I. L., 288.
Williams, A. H. See Hewett, C. L.
Wilson, W. See Catch, J. R.
Woodward, F. N. See Hewett, C. L.

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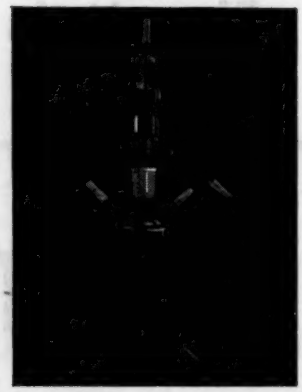

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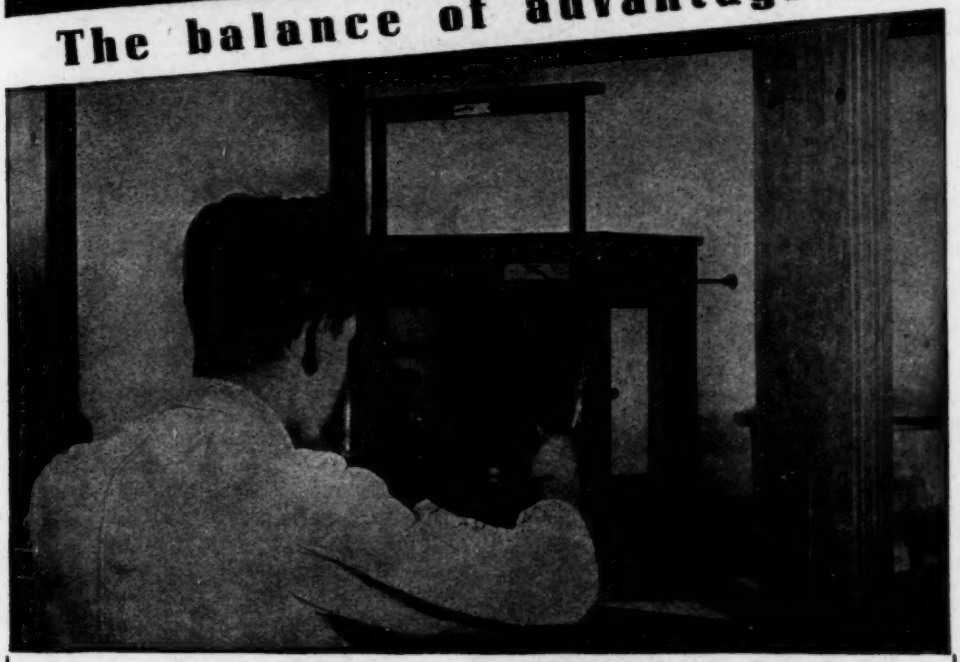

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the Chemical Society in 1883; he was also a Fellow of the Royal Institute of Chemistry and of the Linnean Society, and an honorary member of several foreign pharmaceutical associations.

Hooper was a man of untiring industry, and his modesty and pleasant manner won him many friends at whose disposal he was always ready to place his time and his unique knowledge.

He was all his life a total abstainer and an earnest evangelical Christian deeply concerned with all causes making for the moral and spiritual welfare of mankind. He met his future wife while associated with her father in work for the Union Church at Ootacamund, and on his retirement he spent much time in service to religious organisations in the various localities in which he lived.

T. A. Henry.

GEORGE NEWBERY.

1893—1947.

The death of George Newbery on June 14th, 1947, at the comparatively early age of 54 years, robbed the country of a research worker of great skill and of the kind of gentle, sympathetic, and co-operative personality that is in danger of being banished by the hurly-burly of competitive industrial research to the retreats of academic life. Newbery was born at Brighton in 1893, and was educated at Brighton Grammar School, whence he obtained a scholarship to the Royal College of Science. He graduated with First Class Honours in Chemistry in 1914, and after a few months spent on the semi-scale manufacture of β-eucaine, novocaine, and phenacetin under Professor Jocelyn Thorpe, he obtained a commission in the Royal Engineers (Water Transport) in 1915, and served in France until he was seriously injured in a motor-cycle accident and was invalided out of the Army early in 1918.

In March, 1918, he joined the staff of May & Baker Ltd., and served under Dr. A. J. Ewins, who, in the previous year, had commenced the task of developing a research laboratory for the Company. Newbery's job was his hobby also; long after the official closing time of the factory, he would be found with a colleague or two working late in the laboratory in search for new therapeutic agents or for a synthetic approach to the constitution of known medicinal chemicals. His early work, prompted by the Company's interest in neoarsphenamine, was concerned mainly with organic arsenicals. Many new compounds were produced and examined, and although few of them proved of lasting value and none of them as epoch-making as " N.A.B.", he never lost his interest in this field, and up to the time of his death he was continually on the look-out for some fresh pointer towards the secret of the relationship between chemical constitution and therapeutic activity.

With the discovery of " prontosil rubrum " by Domagk, followed by the French worker's demonstration of sulphanilamide as the active agent, Newbery's attention was drawn to the sulphonamide group, and he and his colleagues, working under the leadership of Dr. Ewins, embarked on a wide new programme of research. Following close upon the heels of the discovery of " M & B 693 ", he produced and examined " M & B 760 ", or sulphathiazole, and its homologues. In collaboration with Sir Lionel Whitby on the bacteriological side, he established the value of this new sulphonamide, which now outrivals its precursor, thanks to a great extent to American workers who were attracted to this field by the success of the British investigators, and who were untrammelled by the imminent outbreak of the Second World War.

When war broke out in 1939, Newbery was among the first to take up Home Guard duties, and his specialised knowledge fitted him for the post of Battalion Gas Officer. But these extra-mural activities were accompanied by added responsibility in his research work which was greatly increased by the new problems raised by war-time shortages and the urgent problems of changing war needs. The formation of the Therapeutic Research Corporation was an event Newbery hailed with much pleasure, since he felt that here was a chance for the pooling of ideas and the widening of team work to the benefit of the nation and the general furtherance of scientific knowledge. He had long had ideas about attacking the problem of the chemotherapeutic treatment of tuberculosis, and he drew up and instituted a plan of work upon which several member firms of the T.R.C. embarked.

Next came the development of the penicillin discovery, and there was added to his formidably wide field an allotted part of the attack on the chemical synthesis of penicillin. There is no doubt that the war years put upon him a strain which was beyond his physical strength to carry, and his serious breakdown in 1945 was unfortunately only the first attack of the illness to which

he succumbed in 1947. He left much of his work unfinished, as indeed must any investigator, cut off suddenly in the midst of his experimentation.

Much of Newbery's work unfortunately did not lend itself to publication, but he was sole or joint author of several papers published in the *Journal* in 1927—28 dealing with organic mercury compounds, and more recently of a series of papers on aromatic diamidines which have proved of considerable chemotherapeutic interest. In addition, his name is associated with numerous patents taken out in conjunction with May & Baker Ltd. during the last 20 years.

His example of quiet, painstaking devotion to duty, his enquiring mind, his willingness to learn of others, and his ability to impart his ideas to others—these qualities live on in the organisation he has helped to build and are the best memorial to the 30 years he spent in its building.

R. W. E. Stickings.

EDGAR PHILIP PERMAN.

1866—1947.

Edgar Philip Perman came of a scholastic family of Wincanton, Somerset, his father, brother, and sister all in their time having been head-teachers. After passing through his father's school, Perman studied under Sir William Ramsay at University College, London, and was awarded the D.Sc. degree of the University of London. He was elected to the Fellowship of the Chemical Society in 1890, and in 1892 became engaged in teaching and research at University College, Cardiff, where he was appointed Assistant Professor in 1904. Here, except for a period of war service in 1914—1918 when he was associated with T. M. Lowry in London in research on ammonium nitrate, he worked until his retirement in 1932. In 1941, after his house had been ruined during an air-raid on Cardiff, he went to live near Builth. After only four days' illness he passed away at Llanafan Fawr on May 27th, 1947, in his 82nd year.

Perman was a lucid, thorough, and painstaking teacher. Among the public of Glamorgan and Monmouthshire he was held in high esteem as an expositor of scientific subjects, and his popular lectures on spinning tops, soap bubbles, and liquid air were given with a wealth of spectacular experiments. It was, however, for his research students that Perman reserved the best of his attention, and he was worthily helped in his investigations by a succession of devoted and skilful workers.

While with Ramsay, Perman carried out research on the boiling points of the alkali metals, the dissociation of diatomic bromine and iodine, and the adiabatic elasticity of ether, but it was after he moved to Cardiff and became an independent worker that he revealed his full ability as a scientific investigator.

Alone and with students, over many years, he worked on the problems of the escape of gases, particularly ammonia, from their solutions. He measured total and partial vapour pressures of solutions over wide ranges of concentration and temperature, and investigated the effect of the presence of salts and non-electrolytes. From his results he calculated activity coefficients and made estimates of the degrees of hydration or of ammoniation of dissolved salts. In the course of this work Perman greatly improved the air-aspiration method, which he also applied to determine the molecular weight of β-naphthol in solid solution in naphthalene, and the dissociation pressure of sodium sulphate decahydrate.

With his students he made very accurate measurements of heats of dilution of solutions, using an electrical method devised for the purpose. He also carried out measurements of the compressibilities of solutions of several substances over wide ranges of concentration.

Almost as early as Haber, Perman realised the importance of the synthesis of ammonia, and using an iron catalyst he demonstrated the reversibility of the reaction, but, owing to the high temperature which he employed, the yield proved discouraging. Another research on gaseous reactions which Perman undertook was the investigation of the effects of solids and vapours on the rate of decomposition of ozone.

From the time of their discovery, Perman took great interest in *X*-rays and radium; he was one of the first to experiment on the possibility of bringing about transmutation of the elements by the aid of radiations, but he demonstrated its impracticability with the means then available.

At the time when it was carried out, Perman's accurate determination of the density of

ammonia was of great value to chemists, for it gave 14·007 as the atomic weight of nitrogen, and confirmed the value which was then being adopted in place of the Stasian 14·04.

In collaboration with other chemists, Perman carried out extensive phase-equilibrium studies on reciprocal salt pairs consisting of ammonium nitrate with the chloride or sulphate of lithium, sodium, or potassium.

Other investigations in which Perman took part were on the use of borax as a standard in acidimetry, on the determination of nitrates by the use of dehydrated potash alum, on the effect of vapours on the interaction of solid potassium iodide and the chlorides of mercury and lead, and on the colour of iron alum crystals.

In manner Perman was quiet, unassuming, and steady. He was a staunch friend and helpful colleague. Absorbed though he was in scientific investigation, Perman was a man of wide interests. He was fond of music, and played both the violin and the pianoforte. He had travelled extensively in Switzerland, Austria, and Germany. When young he was an ardent walker and Alpine climber, and even in his later years visited Switzerland regularly for the ski-ing. He also was a keen motorist and lover of the countryside, and was author of a useful guide-book for motorists, entitled "Highways and Byways in South Wales".

W. J. Jones.

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61. *Constituents of* "Cortex Piscidiæ Erythrinæ." *Part I. The Structure of Piscidic Acid.*

By Walter Bridge, Frederick Coleman, and Alexander Robertson.

Piscidic acid has been shown to be a trihydroxy-dibasic acid, forming acid and neutral esters and an *O*-dimethyl ether. The hydroxyl groups have been proved to be respectively phenolic and secondary and tertiary alcoholic, of which the latter pair are attached to adjacent carbon atoms. Oxidation of *O*-dimethylpiscidic acid and application of the Weerman reaction to the corresponding diamide gave anisaldehyde, whilst degradation of methyl *O*-methylpiscidate by means of lead tetra-acetate yielded *p*-methoxyphenylpyruvic acid. Piscidic acid is shown to have formula (I).

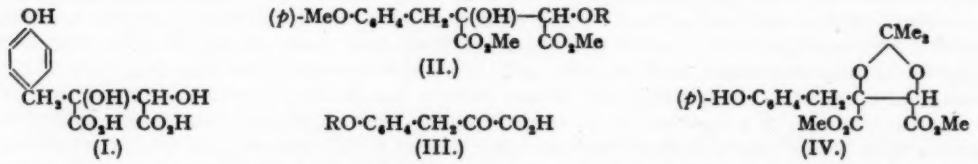
The chemical constituents of this drug, which is the root bark of the tree *Piscidia erythrina* (Linn.) ("Jamaica Dogwood") and was used as a hypnotic and narcotic, have been examined by Hart (*J. Amer. Chem. Soc.*, 1883, **5**, 39), Swaters (*Nederl. Tijdschr. Pharm.*, 1896, **8**, 39), Freer and Clover (*Amer. Chem. J.*, 1901, **25**, 390), Dankwortt and Schütte (*Arch. Pharm.*, 1934, **272**, 701), and Hauschild (*ibid.*, 1936, **274**, 388). Of these the best defined product is the dibasic acid, piscidic acid, $C_{11}H_{12}O_7$, first isolated and examined by Freer and Clover, who prepared a monoethyl ester and its amorphous acetate and also a dianilide, concluding that the substance did not contain an aromatic nucleus and was a dihydroxy-dicarboxylic acid of the aliphatic series in which the carboxyl groups were probably attached to adjacent carbon atoms (positive fluorescein reaction).

Piscidic acid has been isolated by a modification of Freer and Clover's procedure, and their conclusions regarding its empirical formula and basicity have been confirmed. The compound, which does not appear to lose carbon dioxide readily on being heated, has been found to be optically active, does not contain a methoxyl group, is stable to boiling 30% aqueous sodium hydroxide, and behaves as a saturated substance towards hydrogen and a palladium catalyst. Though the acid slowly reduces hot Fehling's solution, all attempts to detect the presence of a carbonyl group gave negative results. By the usual methods it gives *mono-* and *di-methyl* esters of which only the latter gives a ferric reaction, indicating the presence of a phenolic hydroxyl group in agreement with the solubility of the dimethyl ester in dilute aqueous sodium hydroxide; the negative ferric reaction given by the acid and the acid esters appears to be due to the effect of the free carboxyl groups. In the absence of a carbonyl group, conclusive proof that there is a phenolic residue in piscidic acid is afforded by the fact that the acid and its esters react with benzenediazonium chloride in alkaline solution, forming red-brown azo-dyes. Further, the conclusion that piscidic acid contains a benzenoid system is in agreement with the empirical formula and the absence of an easily hydrogenated ethylenic system.

On methylation by the methyl iodide–potassium carbonate method, methyl piscidate invariably gave a *dimethyl ether* of the ester which on hydrolysis yielded *O-dimethylpiscidic acid*. Oxidation of the latter compound with potassium permanganate gave anisic acid, thus showing that the dimethyl ether is a derivative of anisole substituted in the *p*-position by the

group $C_3H_4O(OMe)(CO_2H)_2$ (A), and in the circumstances it appeared that the remaining oxygen atom unaccounted for in the residue (A) was present in an ether system or as an alcoholic hydroxyl group. The presence of the latter group in (A) was quantitatively demonstrated by the application of the Zerewitinoff estimation to methyl *O*-dimethylpiscidate, and, since methyl piscidate gives a tri-acetate but is not apparently converted readily into a trimethyl ether by the methyl iodide–silver oxide method (an amorphous product was obtained, the methoxyl content of which agreed with a dimethyl ether of methyl piscidate), it seemed likely that this hydroxyl group is tertiary, a conclusion in agreement with the positive mercuric sulphate test for a tertiary alcohol given by methyl *O*-dimethylpiscidate. Further, the other alcoholic hydroxyl group present in the side chain is easily methylated, but, as attempts to form a trityl ether of methyl piscidate were unsuccessful, it appeared that this group was secondary, and, moreover, since methyl piscidate readily condenses with acetone in the presence of a dehydrating agent to give an iso*propylidene* derivative, it is reasonably certain that the hydroxyl groups are attached to adjacent carbon atoms. Similarly, the positive fluorescein reaction given by piscidic acid (Free and Clover, *loc. cit.*), which we have confirmed, indicates that the carboxyl groups are also attached to adjacent carbon atoms, and, as it is clear that these groups are contained in the side chain, it seemed likely that piscidic acid was a substituted succinic acid of the type (I) for which there are a number of possible structures.

In the course of numerous degradation experiments carried out to determine the exact structure of the side chain of piscidic acid it was found that the action of hydriodic acid gave only small amounts of an individual substance whilst application of Fenton's reaction, the Oppenauer reaction, and oxidation with lead tetra-acetate or periodic acid to methyl piscidate gave only traces of tractable degradation products. On the other hand the Weerman reaction applied to the *diamide* of *O*-dimethylpiscidic acid furnished anisaldehyde, but all attempts to isolate an intermediate oxidation product were unsuccessful. Similarly, anisaldehyde was also formed when methyl *O*-dimethylpiscidate was oxidised with chromic oxide. Since it seemed reasonably certain that piscidic acid was a 1 : 2-glycol which normally would be expected to be degraded with lead tetra-acetate or periodic acid, the failure of methyl piscidate to yield definite products with these reagents appeared to be due to the interference of the free phenolic hydroxyl group. After numerous attempts by other methods it was found that methyl piscidate could be mono-methylated or -benzylated by the action of methyl iodide or benzyl bromide, respectively, on its sodio-derivative, thus giving *monomethyl* and *monobenzyl ethers* of methyl piscidate which are insoluble in aqueous sodium hydroxide. Oxidation of the monomethyl ether with lead tetra-acetate in acetic acid gave rise to a crystalline compound, the nature of which has not yet been fully investigated, but which on hydrolysis with boiling alcoholic potassium hydroxide gave *p*-methoxyphenylpyruvic acid (III, R = Me) with a small amount of anisaldehyde. Similarly, oxidation of the monobenzyl ether yielded a crystalline product which on being hydrolysed gave p-*benzyloxyphenylpyruvic acid* (III, R = Ph·CH_2), identical with an authentic specimen. A more detailed examination of the optically inactive primary oxidation products formed by lead tetra-acetate will be made when material is available.



The production of (III, R = Me) from (II, R = H) by lead tetra-acetate clearly indicates the presence of a *p*-hydroxybenzyl residue in piscidic acid, and hence, in agreement with the view that the side chain is a substituted succinic acid residue in which two hydroxyl groups have been shown to be attached to adjacent carbon atoms, it seems reasonably certain that methyl *O*-methylpiscidate has formula (II, R = H). Consequently piscidic acid is *p*-hydroxybenzyltartaric acid (I), forming the dimethyl ether (II, R = Me) and the *iso*propylidene derivative (IV) of the methyl ester.

Experimental.

Piscidic Acid.—Pulverised root bark of *Piscidia erythrina* (1350 g.) was extracted with water (13·5 l. (agitate) for 4 days and the filtered extract concentrated to one-fourth of its volume, treated with charcoal, and filtered. Sufficient saturated lead acetate solution was added to this liquor to precipitate a small amount of colouring matter as a dark brown solid, leaving a pale straw-coloured liquid which

on filtration and subsequent treatment with an excess of the reagent gave a precipitate of the almost colourless lead salt of piscidic acid. The solid was washed by decantation, collected, suspended in alcohol, and decomposed with excess of hydrogen sulphide and, after removal of the lead sulphide by filtration, the alcoholic liquor was evaporated under reduced pressure, leaving crude piscidic acid as a straw-coloured crystalline solid contaminated with resinous material. A solution of this product in a slight excess of boiling ethyl acetate was treated with a little warm chloroform, and, after having been decanted from the resinous material which first separated, the hot liquid was treated with an equal volume of boiling chloroform; the optimum proportions of ethyl acetate and chloroform were found by trial for each batch of crude acid. On cooling, the solution deposited piscidic acid in elongated colourless prisms which on recrystallisation had m. p. 183—184° and, after having been dried in a high vacuum at 110—115°, m. p. 186—187°, $[\alpha]_D^{20°}$ +41·03° (*c*, 2·65 in water) (Found: C, 51·0; H, 5·0; *M*, 258. Calc. for $C_{11}H_{12}O_7$: C, 51·6; H, 4·7%; *M*, 256) (Freer and Clover, *loc. cit.*, give m. p. 182—185°).

On being boiled with alcohol (50 c.c.) containing 10 drops of concentrated hydrochloric acid and subsequent removal of the solvent, piscidic acid (2 g.) gave the monoethyl ester (1·3 g.) which separated from warm water and then ethyl acetate–chloroform in slender colourless needles, m. p. 211—212° (Freer and Clover record m. p. 207—208°) (Found: C, 54·9; H, 5·7. Calc. for $C_{13}H_{16}O_7$: C, 54·9; H, 5·6%). This derivative, which is soluble in alcohol, acetone, or ethyl acetate, and insoluble in chloroform, dissolves in aqueous sodium hydrogen carbonate with evolution of carbon dioxide. Prepared by the same procedure, the *monomethyl* ester formed slender colourless needles, m. p. 179°, from ethyl acetate–chloroform, having similar solubilities (Found in material dried in a high vacuum at 110°: C, 52·6; H, 5·5; *M*, 254. $C_{12}H_{14}O_7$ requires C, 53·1; H, 5·5%; *M*, 270). Interaction of this ester (2·5 g.) with ethereal diazomethane (from 3 c.c. of nitrosomethylurethane) for 5 minutes gave the *dimethyl* ester (2·3 g.), forming colourless prisms, m. p. 127°, from benzene and having a bottle-green ferric reaction in aqueous solution (Found: C, 55·1; H, 5·7; *M*, 294. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·6%; *M*, 284). The same ester, m. p. and mixed m. p. 127°, was obtained by action of excess of diazomethane on piscidic acid and by esterification of the acid (3 g.) in boiling absolute methyl alcohol (100 c.c.) containing 10 g. of sulphuric acid during 12 hours. Acetylation of this ester (1 g.) with pyridine (2·5 ml.) and acetic anhydride (5 ml.) at room temperature during 36 hours gave a glass which did not crystallise but, on being refluxed with acetic anhydride (6 ml.) and sodium acetate (1 g.) for 20 minutes, yielded the *triacetate* (0·8 g.), forming a mat of slender needles, m. p. 84°, from light petroleum (b. p. 60—80°) and having a negative ferric reaction [Found: C, 55·9; H, 5·6; Ac, 32·2. $C_{13}H_{13}O_4(OAc)_3$ requires C, 55·6; H, 5·4; Ac, 31·4%]. The same product was obtained directly from the ester by means of boiling acetic anhydride and sodium acetate.

A solution of methyl piscidate (1 g.) in 2% aqueous sodium hydroxide (7 ml.) was vigorously agitated with ether (15 ml.) containing (0·5 ml.) of acetic anhydride for 15 minutes, the ether was separated, and the residual liquor extracted several times with fresh solvent. Evaporation of the combined washed and dried ethereal extracts left the *monoacetate* of methyl piscidate which formed elongated rectangular prisms, m. p. 117—118°, from water, having a negative ferric reaction [Found: C, 55·4; H, 5·7; OMe, 18·8; Ac, 13·5. $C_9H_7O_5(OMe)_3(OAc)$ requires C, 55·2; H, 5·2; OMe, 19·0; Ac, 13·2%].

O-*Dimethylpiscidic Acid.*—Treatment of methyl piscidate with excess of diazomethane during 5 hours gave only unchanged material, but methylation of the ester (3 g.) in boiling acetone (90 ml.) with methyl iodide (5 ml.) and potassium carbonate (6 g.) for 10 hours, with the addition of more iodide (3 ml.) and carbonate (3 g.) after 5 hours, furnished the *dimethyl ether* (II, R = Me) (1·8 g.) of the ester which separated from methyl alcohol in elongated prisms, m. p. 115°, having a negative ferric reaction [Found: C, 57·8; H, 6·5; OMe, 39·5. $C_{11}H_9O_3(OMe)_4$ requires C, 57·7; H, 6·4; OMe, 39·7%]. Hydrolysis of this dimethyl ether (1 g.) with potassium hydroxide (1·1 g.) in alcohol (10 ml.) and water (10 ml.) at room temperature (agitate) for 4 hours yielded O-*dimethylpiscidic acid* which formed colourless rectangular prisms (0·7 g.), m. p. 177°, from ethyl acetate or light petroleum (b. p. 60—80°), having a negative ferric reaction [Found: C, 55·1; H, 5·7; OMe, 21·6. $C_{11}H_{10}O_7(OMe)_2$ requires C, 54·9; H, 5·6; OMe, 21·8%]. Acidification of the potassium carbonate residues from the foregoing methylation gave small amounts of this acid.

When a solution of methyl *O*-dimethylpiscidate (2 g.) in methyl alcohol (60 ml.) was saturated with ammonia and kept at room temperature for 4 days and the excess of ammonia and alcohol then removed under reduced pressure, an almost theoretical yield of the *diamide* was obtained. This separated from ethyl acetate or chloroform in squat prisms, m. p. 156° [Found: C, 55·3; H, 6·5; N, 9·6; OMe, 22·1. $C_{11}H_{12}O_2N_2(OMe)_2$ requires C, 55·3; H, 6·4; N, 9·9; OMe, 22·0%].

Methyl O-*Methylpiscidate* (II, R = H).—A solution of methyl piscidate (1 g.) in alcohol (15 ml.), containing sodium ethoxide (from 0·4 g. of sodium) and methyl iodide (1·5 ml.), was refluxed for 2·5 hours and the cooled solution diluted with excess of ether, washed twice with 2% aqueous sodium hydroxide (8 ml.) and then with water, and dried. Removal of the solvent left the *monomethyl ether* which formed elongated rectangular prisms (0·4 g.), m. p. 110—111°, having a negative ferric reaction [Found: C, 56·6; H, 6·0; OMe, 30·9. $C_{11}H_9O_4(OMe)_3$ requires C, 56·4; H, 6·1; OMe, 31·2%]. A lower yield of the same product was obtained when methyl alcohol was used as the solvent, thus showing that there had been no interchange of radical in either of the ester groups by the use of ethyl alcohol as a solvent.

When the methyl iodide was replaced by benzyl bromide (6 ml.) in the foregoing alkylation a good yield of the corresponding *monobenzyl ether* was obtained which, on repeated crystallisation from dilute alcohol, formed slender rods, m. p. 100° (Found: C, 64·3; H, 6·2. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%).

iso*Propylidene Derivative of Methyl Piscidate* (IV).—A mixture of methyl piscidate (1 g.), acetone (25 ml.), and concentrated sulphuric acid (1 ml.) was kept for 3 hours, the resulting red mixture was neutralised with dry sodium hydrogen carbonate, the salts were removed by filtration (wash with acetone), and the solvent was evaporated under reduced pressure. A solution of the amber-coloured residual oil in ether was washed, dried, and evaporated, leaving the iso*propylidene* derivative (0·65 g.) which formed prisms, m. p. 140°, from dilute alcohol or carbon tetrachloride, readily soluble in chloro-

form, benzene, or ethyl acetate [Found: C, 58·9; H, 6·0; OMe, 18·8. $C_{14}H_{14}O_5(OMe)_2$ requires C, 59·3; H, 6·2; OMe, 19·1%]. Hydrolysis of this compound with warm dilute hydrochloric acid gave acetone which was characterised by the formation of its 2 : 4-dinitrophenylhydrazone, m. p. 124°, identified by comparison with an authentic specimen.

Oxidation of Piscidic Acid Derivatives.—(*a*) To a solution of *O*-dimethylpiscidic acid, obtained by the hydrolysis of the methyl ester (1 g.) with 1% aqueous sodium hydroxide (10 ml.), 3% aqueous potassium permanganate was gradually added during 4 hours until the permanganate colour persisted. Next day the solution was cleared with sulphur dioxide, the liquor was saturated with ammonium sulphate and repeatedly extracted with ether, and the dried ethereal extracts were evaporated, leaving an acid which on crystallisation from water and then benzene gave slender rectangular prisms, m. p. 183—184°, identical in every way with an authentic specimen of anisic acid [Found: C, 63·1; H, 5·3; OMe, 20·3; *M* (by titration), 150·9. Calc. for $C_7H_5O_2(OMe)$: C, 63·2; H, 5·3; OMe, 20·4%; *M*, 152]. Prepared by means of diazomethane, the methyl ester had m. p. 48°, undepressed on admixture with an authentic specimen [Found: C, 65·1; H, 6·1; OMe, 37·1. Calc. for $C_7H_4O(OMe)_2$: C, 65·1; H, 6·0; OMe, 37·4%].

(*b*) Suspended in water (40 ml.) at 0°, the diamide of *O*-dimethylpiscidic acid (1 g.), was treated with aqueous sodium hypochlorite (11 ml. of a solution containing 5·5% of available chlorine) and the mixture maintained at 0° for 2 days. After the removal of unchanged amide (0·35 g.) by filtration, the solution was acidified and extracted several times with ether. Treatment of an alcoholic solution of the oil left on evaporation of the ether with 2 : 4-dinitrophenylhydrazine hydrochloride solution gave the 2 : 4-dinitrophenylhydrazone of anisaldehyde, forming vermilion plates, m. p. 250° (decomp.), identical with an authentic specimen [Found: C, 53·5; H, 3·8; N, 17·8; OMe, 9·8. Calc. for $C_{14}H_{12}O_5N_4$; C, 53·2; H, 3·8; N, 17·7; OMe, 9·8%]. Oxidation of the crude reaction product with aqueous potassium permanganate gave anisic acid, m. p. and mixed m. p. 183—184°.

(*c*) Oxidation of *O*-dimethylpiscidic acid (1 g.) in water (15 ml.) with chromic oxide (0·5 g.) in water (5 ml.) during 2¼ hours with subsequent addition of methyl alcohol (5 ml.) to destroy unchanged chromic acid gave, on isolation of the product with ether, anisaldehyde which was characterised by the formation of its 2 : 4-dinitrophenylhydrazone, m. p. 250° (decomp.).

(*d*) A solution of methyl *O*-methylpiscidate (II, R = H) (1 g.) and lead tetra-acetate (1·55 g.) in acetic acid (25 ml.) was kept for 24 hours, diluted with water (75 ml.), and repeatedly extracted with ether. The combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate to remove acetic acid, dried, and evaporated, leaving a colourless crystalline residue (0·8 g.). Recrystallised from benzene or benzene–light petroleum (b. p. 60—80°), this compound formed angular prisms (0·55 g.), m. p. 129°, which had an intense green ferric reaction in alcohol and was optically inactive [Found: C, 60·6; H, 4·6; OMe, 29·4%]. A solution of the compound (1·5 g.) in alcohol (33 ml.) containing potassium hydroxide (1·8 g.) was refluxed for 2½ hours, acidified with dilute hydrochloric acid, and extracted with ether. After the removal of acidic material from the combined ethereal extracts, the latter were dried and evaporated, leaving a small quantity of anisaldehyde, identified by conversion into the 2 : 4-dinitrophenylhydrazone. Acidification of the sodium hydrogen carbonate washings gave an acid which separated from acetic acid in elongated prisms (0·35 g.), m. p. 179° (decomp.), having an intense green ferric reaction, and was identified as *p*-methoxyphenylpyruvic acid by comparison with an authentic specimen [Found: C, 62·0; H, 5·5; OMe, 16·0. Calc. for $C_9H_7O_3(OMe)$: C, 61·9; H, 5·2; OMe, 16·0%]. This compound formed an oxime which separated from benzene in rectangular prisms, m. p. 157° (decomp.), identical with the oxime of *p*-methoxyphenylpyruvic acid [Found: C, 57·8; H, 5·4; N, 6·8; OMe, 15·1. Calc. for $C_9H_8O_3N(OMe)$: C, 57·4; H, 5·2; N, 6·7; OMe, 14·8%]. The methyl ester, colourless prisms from aqueous methyl alcohol, had m. p. 95°, undepressed on admixture with an authentic specimen.

(*e*) (With J. B. D. McKenzie.) Methyl *O*-benzylpiscidate (1 g.) was oxidised with lead tetra-acetate and the product isolated by the procedure employed in (*d*). Crystallised from benzene, the latter substance was obtained in long slender needles, m p. 157°, soluble in alcohol or ethyl acetate and insoluble in aqueous sodium hydrogen carbonate and having a dark green ferric reaction in alcohol (Found: C, 67·9; H, 5·4%; *M*, 303). Hydrolysis of this substance, which was optically inactive, in boiling 5% aqueous-alcoholic sodium hydroxide for 2 hours yielded p-*benzyloxyphenylpyruvic acid* which, on purification by means of aqueous sodium hydrogen carbonate and then by crystallisation from a little acetic acid or from 50% acetic acid, formed clusters of prisms, m. p. 192°, after sintering at 180—182°, identical with a synthetical specimen prepared by the following method. Hydrolysis of 4-(4′-acetoxybenzylidene)-2-methyl-5-oxazolone (Dakin, *J. Biol. Chem.*, 1929, **82**, 439) (1 g.) with 1·5N-hydrochloric acid (20 ml.) at 100° for 4 hours gave *p*-hydroxyphenylpyruvic acid (0·6 g.), m. p. 220°, after purification (cf. Neubauer and Fromberg, *Z. physiol. Chem.*, 1910, **70**, 326), which on esterification with methyl alcohol and hydrogen chloride gave the methyl ester as a low melting solid, b. p. 125°/0·03 mm. The ester was characterised by the formation of the 2 : 4-*dinitrophenylhydrazone* which separated from ethyl acetate in pale yellow rhombs, m. p. 201° (Found: C, 51·2; H, 3·5; N, 15·1. $C_{16}H_{14}O_7N_4$ requires C, 51·3; H, 3·7; N, 15·0%). Prepared by the benzyl bromide–potassium carbonate method, the *p*-benzyl ether of this ester was obtained as an oil, forming a 2 : 4-*dinitrophenylhydrazone* which crystallised from ethyl acetate in scarlet needles, m. p. 226—227° (Found: C, 59·6; H, 4·5; N, 12·1. $C_{22}H_{20}O_7N_4$ requires C, 59·5; H, 4·3; N, 12·1%). On hydrolysis with 5% aqueous alcoholic potassium hydroxide this compound gave p-*benzyloxyphenylpyruvic acid* which was isolated with ether and purified by crystallisation from 50% acetic acid, forming colourless prisms, m. p. 192° after sintering at 180—182° (Found: C, 70·9; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%). This compound had a green ferric reaction in alcohol.

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University of Liverpool. [*Received, March 17th*, 1947.]

62. *Attempts to find New Chemotherapeutic Amidines. Part IX. Derivatives of* 1 : 1-*Diphenylethylene and Naphthalene.*

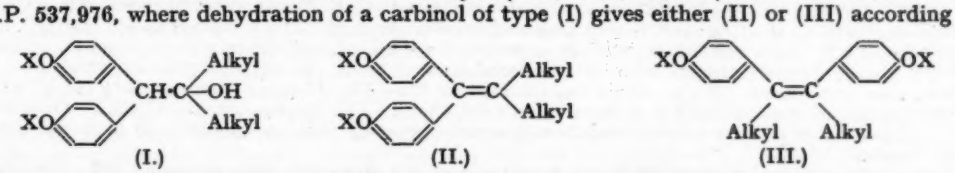
By J. N. Ashley, J. F. Grove, and T. Henshall.

4 : 4′-Diamidino-derivatives of 1 : 1-diphenylethylene, 1 : 1-diphenyl-2-methyl-, and 1 : 1-diphenyl-2 : 2-dimethylethylene, and 6 : 6′-diamidino-derivatives of 1 : 3-di-β-naphthoxypropane, 1 : 5-di-β-naphthoxypentane, and 2 : 2′-dimethoxy-1 : 1′-dinaphthylmethane have been prepared. These products exhibited little or no trypanocidal activity.

Previous papers from these laboratories have described the synthesis of diamidino-derivatives of stilbene and of substituted stilbenes (Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103; Barber, Slack and Woolman, *J.*, 1943, 99; Barber and Slack, *J.*, 1944, 612; Ashley and Harris, *J.*, 1946, 567). In view of the trypanocidal activities of 4 : 4′-diamidinostilbene (" Stilbamidine ") (Kirk and Sati, *Ann. Trop. Med. Parasitol.*, 1940, **34**, 83; Napier, Sen Gupta, and Sen, *Indian Med. Gaz.*, 1942, **77**, 321) and of 4 : 4′-diamidino-αβ-dimethylstilbene (Fulton and Yorke, *Ann. Trop. Med. Parasitol.*, 1942, **36**, 131), it was decided to examine the properties of the isomeric compounds derived from 1 : 1-diphenylethylene, and to determine what effect, if any, was caused by the isomerism. Also, since 4′ : 4″-diamidino-1 : 3-diphenoxypropane (" Propamidine ") and 4′ : 4″-diamidino-1 : 5-diphenoxypentane (" Pentamidine ") are active trypanocidal agents, it was considered desirable to prepare the corresponding derivatives of naphthalene and ascertain what effect the extra benzene ring had on the activity.

Stoermer and Simon (*Ber.*, 1904, **37**, 4168) described the preparation of 4′-bromo-1 : 1-diphenylethylene by reaction of 4-bromobenzophenone with methylmagnesium iodide and decomposition of the resulting carbinol by distillation under reduced pressure. 4′ : 4″-*Dibromo*-1 : 1-*diphenylethylene*, 4′ : 4″-*dibromo*-1 : 1-*diphenyl*-2-*methylethylene*, and 4′ : 4″-*dibromo*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene* were prepared by analogous reactions from 4 : 4′-dibromobenzophenone and methyl, ethyl, and *iso*propyl halides respectively. These dibromo-compounds were converted into the corresponding *dicyanides* by heating with cuprous cyanide in pyridine, and thence by the usual method into the diamidines (*hydrochlorides*), the salts of which were considerably more soluble in water than those of the isomeric, symmetrical compounds derived from stilbene. Each of the three diamidines was very slightly active trypanocidally, and hence isomerisation of the symmetrical stilbene into the unsymmetrical 1 : 1-diphenylethylene is accompanied by loss of trypanocidal activity in the diamidino-derivatives.

In view of the results of Foldi and Demjen (*Ber.*, 1941, **74**, 930) and those described in B.P. 537,976, where dehydration of a carbinol of type (I) gives either (II) or (III) according to



(I.) (II.) (III.)

whether the dehydration is effected with dilute acid or by boiling in toluene with phosphorus oxychloride, it was considered of interest to determine whether any radical migration occurred, with formation of 4 : 4′-dibromo-αβ-dimethylstilbene, when 4′ : 4″-dibromo-1 : 1-diphenyl*iso*propylcarbinol was dehydrated by heating in toluene solution with phosphorus oxychloride. No migration occurred and only 4′ : 4″-dibromo-1 : 1-diphenyl-2 : 2-dimethylethylene was isolated.

Several unsuccessful attempts were made to prepare 4′ : 4″-dibromo-1 : 1-diphenyl-2 : 2-diethylethylene by interaction of 4 : 4′-dibromobenzophenone with *iso*amyl bromide and subsequent dehydration, but reduction of the ketone occurred and only 4 : 4′-dibromobenzhydrol was isolated. This accords with the results of Davies, Dixon, and Jones (*J.*, 1930, 1916) on the reaction of benzophenone with *iso*amyl bromide. Similarly substitution of cetyl bromide for *iso*amyl bromide (with the object of synthesising a diamidine which might be soluble in oil) led to reduction of the ketone, and formation of a wax-like hydrocarbon.

The only diamidino-derivatives of naphthalene which were known at the time when this work was in progress were 2 : 6- and 2 : 7-diamidinonaphthalene (King and Wright, *J.*, 1939, 253); these exhibited trypanocidal activity. In view of the activity of 4′ : 4″-diamidino-1 : 3-diphenoxypropane and 4′ : 4″-diamidino-1 : 5-diphenoxypentane it was decided to attempt the synthesis of the corresponding naphthalene homologues. 1 : 5-*Di*-α-*naphthoxypentane*, prepared by condensation of α-naphthol with pentamethylene dibromide, was readily brominated in

chloroform at room temperature to 2′ : 2″ : 4′ : 4″-*tetrabromo-*, or in more dilute solution at a lower temperature to 4′ : 4″-*dibromo*-1 : 5-*di*-α-*naphthoxypentane* [cf. bromination of anisole (Michaelis and Weitz, *Ber.*, 1887, **20**, 49; Bodroux, *Compt. rend.*, 1903, **136**, 378); bromination of 1-naphthyl ethyl ether (Marchetti, *Gazzetta*, 1879, **9**, 544); bromination of diphenyl ether (Maihle and Murat, *Compt. rend.*, 1912, **154**, 603; Le Fèvre, Saunders, and Turner, *J.*, 1927, 1169)]. Reaction of the latter with cuprous cyanide in pyridine yielded 4′ : 4″-*dicyano*-1 : 5-*di*-α-*naphthoxypentane*. No attempt was made to prepare the di-iminoether since these are not readily formed from 1-cyanonaphthalenes, and application of the sodamide method (Ewins *et al.*, B.P. 538,463) failed to yield any appreciable quantity of basic material.

6-Bromo-2-naphthol, prepared by reduction of 1 : 6-dibromo-2-naphthol (Fries and Schimmelschmidt, *Ber.*, 1925, **58**, 2840), was condensed with trimethylene and pentamethylene dibromides giving 6′ : 6″-*dibromo*-1 : 3-*di*-β-*naphthoxypropane* and 6′ : 6″-*dibromo*-1 : 5-*di*-β-*napthoxypentane* respectively. These were converted into the *dicyanides* by reaction with cuprous cyanide in pyridine and thence by the usual method into the corresponding diamidines.

6-Bromo-2-methoxynaphthalene condensed readily with formaldehyde in acid solution to give 6′ : 6″-*dibromo*-2′ : 2″-*dimethoxydi*-α-*naphthylmethane*, which was converted by the usual method into 6′ : 6″-*dicyano*- and 6′ : 6″-*diamidino*-2′ : 2″-*dimethoxydi*-α-*naphthylmethane*.

The above diamidino-derivatives of naphthalene formed hydrochlorides which were only very slightly soluble in water, and the solutions exhibited a marked tendency to form gels. None exhibited any significant trypanocidal activity.

An unsuccessful attempt was also made to prepare a diamidino-derivative of a dinaphthylethylene. 6-Bromo-2-methoxynaphthalene readily underwent chloromethylation yielding 6-*bromo*-2-*methoxy*-1-*chloromethylnaphthalene*. The chlorine atom in this compound was extremely reactive, and a few minutes' heating with methyl alcohol was sufficient to yield the corresponding methyl ether. Cook, Downer, and Hornung (*J.*, 1941, 502) described the preparation of 2 : 2′-dimethoxydi-α-naphthylethylene by reaction of 2-methoxy-1-chloromethylnaphthalene with silver nitrate, but the reaction of 6-bromo-2-methoxy-1-chloromethylnaphthalene with silver nitrate followed a very different course,* and no 6 : 6′-dibromo-2 : 2′-dimethoxydi-α-naphthylethylene was formed.

Experimental.

4 : 4′-*Dibromobenzophenone*.—This was prepared by bromination of diphenylmethane followed by oxidation with chromic acid, as described by Goldthwaite (*Amer. Chem. J.*, 1903, **30**, 448). The product (overall yield 20—25%) had m. p. 173°.

4′ : 4″-*Dibromo*-1 : 1-*diphenylethylene*.—Finely powdered 4 : 4′-dibromobenzophenone (62 g.) was added gradually to the Grignard reagent prepared from magnesium (7·9 g.), methyl iodide (44·5 g.), and ether (150 c.c.). After the initial reaction, more ether was added, and the mixture was gently refluxed for 0·5 hour. After treatment with ice and ammonium chloride, the ethereal solution yielded an oil which soon crystallised (70 g.). This was distilled at 224—230°/15 mm.; the distillate (44 g.) after crystallisation from alcohol had m. p. 84° (Found : Br, 49·0. $C_{14}H_{10}Br_2$ requires Br, 47·5%). Oxidation with chromic acid yielded 4 : 4′-dibromobenzophenone, showing that no migration of a phenyl group had occurred.

4′ : 4″-*Dicyano*-1 : 1-*diphenylethylene*.—A mixture of the above dibromo-compound (45 g.) cuprous cyanide (33 g.), and pyridine (33 c.c.) was heated at 200—220° (internal temp.) for 1·75 hours. The cold melt was extracted several times with hot hydrochloric acid (*d* 1·16), and the residue finally crystallised thrice from alcohol. The *dicyanide* crystallised in pale yellow prisms, m. p. 158—160° (Found : N, 11·9. $C_{16}H_{10}N_2$ requires N, 12·2%).

4′ : 4″-*Diamidino*-1 : 1-*diphenylethylene*.—The *dihydrochloride* was prepared *via* the di-iminoether dihydrochloride by the usual method. It crystallised from dilute hydrochloric acid in colourless plates or needles (Found : N, 15·2; Cl, 19·0. $C_{16}H_{16}N_4,2HCl,2H_2O$ requires N, 15·1; Cl, 19·0%).

4′ : 4″-*Dibromo*-1 : 1-*diphenyl*-2-*methylethylene*.—This was prepared similarly to the diphenyl derivative by using 4 : 4′-dibromobenzophenone (58 g.), magnesium (8 g.), ethyl iodide (52 g.), and ether (250 c.c.). The *compound* was a colourless oil (40 g.), b. p. 144—148°/0·08 mm. After removal of a small amount of unchanged ketone by treatment with Girard-T reagent, it crystallised from alcohol in colourless needles or long prisms, m. p. 64—66° (Found : Br, 45·0, 45·3. $C_{15}H_{12}Br_2$ requires Br, 45·45%).

4′ : 4″-*Dicyano*-1 : 1-*diphenyl*-2-*methylethylene*.—This was prepared by the usual method from the above dibromo-compound (7 g.), cuprous cyanide (7 g.), and pyridine (4 c.c.). The *dicyanide* (3·3 g.), purified by distillation under reduced pressure, crystallised from alcohol in colourless prisms, m. p. 120—122° (Found : N, 11·45. $C_{17}H_{12}N_2$ requires N, 11·5%).

4′ : 4″-*Diamidino*-1 : 1-*diphenyl*-2-*methylethylene*.—This was prepared by the usual method from the cyanide (3 g.) in a mixture of chloroform (12 c.c.) and alcohol (5 c.c.). The *dibenzoate* crystallised from 50% aqueous alcohol in clusters of prisms or needles, m. p. 276° (decomp.) (Found : N, 10·3. $C_{17}H_{16}N_4,2C_7H_6O_2$ requires N, 10·7%).

4′ : 4″-*Dibromo*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene*.—This was prepared similarly to the monomethyl

* This reaction, and the behaviour of related compounds, will be described by one of us (J. N. A.) in a subsequent communication.

derivative but from 4 : 4′-dibromobenzophenone (50 g.), magnesium (5·4 g.), *iso*propyl bromide (27 g.), and ether (125 c.c.). The *product* (37 g.) had b. p. 120°/21 mm. and crystallised from alcohol in colourless plates, m. p. 96° (Found : Br, 43·8. $C_{18}H_{14}Br_2$ requires Br, 43·7%).

In another experiment the reaction mixture was not heated, and after decomposition of the Grignard complex, the ether was removed at a low temperature. Part of the semi-solid material (5 g.) was boiled for 4 hours with toluene (15 c.c.) and phosphorus oxychloride (50 g.). After cooling, the mixture was poured on ice, and the toluene layer separated and dried (sodium sulphate). After removal of toluene under reduced pressure, the product was crystallised from alcohol; it melted at 94—95° and was shown by direct comparison to be 4′ : 4″-dibromo-1 : 1-diphenyl-2 : 2-dimethylethylene. Hence dehydration of the carbinol with phosphorus oxychloride had not caused any rearrangement.

4′ : 4″-*Dicyano*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene*.—This was made by the usual method from the above dibromo-compound (36 g.), cuprous cyanide (22·5 g.), and pyridine (23 c.c.). The *dicyanide* (13 g.) had b. p. 284°/27 mm., and crystallised from methyl alcohol in colourless plates, m. p. 90° (Found : N, 10·8. $C_{18}H_{14}N_2$ requires N, 10·85%).

4′ : 4″-*Diamidino*-1 : 1-*diphenyl*-2 : 2-*dimethylethylene*.—The *dihydrochloride* crystallised from methyl alcohol–acetone in small prisms (Found : N, 14·0; Cl, 17·8. $C_{18}H_{20}N_4,2HCl,2H_2O$ requires N, 13·95; Cl, 17·7%).

1 : 5-*Di-α-naphthoxypentane*.—α-Naphthol (14·4 g.) was boiled in alcohol (50 c.c.) containing sodium ethoxide (from 2·3 g. of sodium) with pentamethylene dibromide (11·5 g.) for 3 hours. After removal of the alcohol, the *compound* was extracted with boiling light petroleum (b. p. 60—80°) and then recrystallised twice from alcohol. It separated in glistening colourless plates (4 g.), m. p. 80—81° (Found : C, 83·8; H, 6·5. $C_{25}H_{24}O_2$ requires C, 84·3; H, 6·7%).

4′ : 4″-*Dibromo*-1 : 5-*di-α-naphthoxypentane*.—Bromine (5·6 g.) in chloroform (40 c.c.) was added slowly to a stirred ice-cold solution of 1 : 5-di-α-naphthoxypentane (6 g.) in chloroform (40 c.c.). The temperature was then allowed to rise slowly to 15°. Evaporation of the chloroform gave the *compound*, which crystallised from acetone in colourless prisms, m. p. 100° (Found : Br, 31·0. $C_{25}H_{22}O_2Br_2$ requires Br, 31·1%).

2′ : 2″ : 4′ : 4″-*Tetrabromo*-1 : 5-*di-α-naphthoxypentane*.—Bromine (2·8 g.) in chloroform (5 c.c.) was added to 1 : 5-di-α-naphthoxypentane (3 g.) in chloroform (5 c.c.). Rapid reaction occurred and the *tetrabromo*-compound soon crystallised. It formed colourless needles from chloroform–alcohol, m. p. 136° (Found : Br, 47·35. $C_{25}H_{20}O_2Br_4$ requires Br, 47·5%).

4′ : 4″-*Dicyano*-1 : 5-*di-α-naphthoxypentane*.—A mixture of the above dibromo-compound (2·6 g.), cuprous cyanide (1 g.), and pyridine (1 c.c.) was heated at 180—200° for 1·5 hours. The reaction mixture was extracted with cold hydrochloric acid (*d* 1·16) and the crude *dicyanide* (1·9 g.) crystallised from acetic acid; m. p. 177° (Found : N, 7·05. $C_{27}H_{22}O_2N_2$ requires N, 6·9%).

6′ : 6″-*Dibromo*-1 : 3-*di-β-naphthoxypropane*.—A mixture of 6-bromo-2-naphthol (20 g.) in alcohol (60 c.c.), potassium hydroxide (5 g.) in water (10 c.c.), and trimethylene dibromide (10 g.) was boiled under reflux for 20 hours. After removal of most of the alcohol, and addition of water, the pasty solid was washed with ether. The *product* (12 g.) crystallised from glacial acetic acid in long flat prisms, m. p. 177° (Found : Br, 32·8. $C_{23}H_{18}O_2Br_2$ requires Br, 32·9%).

6′ : 6″-*Dicyano*-1 : 3-*di-β-naphthoxypropane*.—A mixture of the dibromo-compound (7 g.), cuprous cyanide (3·5 g.), and pyridine (3 c.c.) was heated for 2 hours while the temperature of the melt was maintained at 200—210°. The *dicyanide* was worked up in the usual way and crystallised from glacial acetic acid in colourless needles (3·5 g.), m. p. 220—222° (Found : N, 7·3. $C_{25}H_{18}O_2N_2$ requires N, 7·4%).

6′ : 6″-*Diamidino*-1 : 3-*di-β-naphthoxypropane*.—This was prepared by the usual method from the dicyanide. The *di-isethionate* crystallised from alcohol–acetone; m. p. 259° (Found : N, 8·2. $C_{23}H_{24}O_2N_4,2C_2H_6O_4S$ requires N, 8·4%).

6′ : 6″-*Dibromo*-1 : 5-*di-β-naphthoxypentane*.—A mixture of 6-bromo-2-naphthol (20 g.) in alcohol (50 c.c.), potassium hydroxide (5 g.) in water (10 c.c.), and pentamethylene dibromide (10·5 g.) was boiled under reflux for 20 hours. The *product* (16 g.) was isolated by removal of most of the alcohol and addition of water. It crystallised from acetic acid in colourless needles, m. p. 147—148° (Found : Br, 30·5. $C_{25}H_{22}O_2Br_2$ requires Br, 31·1%).

6′ : 6″-*Dicyano*-1 : 5-*di-β-naphthoxypentane*.—This was prepared by the usual method from the dibromo-compound (5 g.), cuprous cyanide (2·2 g.), and pyridine (3 c.c.). The *dicyano*-compound (2·8 g.) crystallised from acetic acid in colourless prisms, m. p. 182—183° (Found : N, 7·0. $C_{27}H_{22}O_2N_2$ requires N, 6·9%).

6′ : 6″-*Diamidino*-1 : 5-*di-β-naphthoxypentane*.—The *dihydrochloride* crystallised from dilute hydrochloric acid in fine fibres, m. p. 245° (Found : N, 9·9. $C_{27}H_{28}O_2N_4,2HCl,2H_2O$ requires N, 10·2%). The *di-isethionate* crystallised in colourless fibres from methyl alcohol–acetone, m. p. 194—195° (Found : N, 7·7. $C_{27}H_{28}O_2N_4,2C_2H_6O_4S,2H_2O$ requires N, 7·7%).

6 : 6′-*Dibromo*-2 : 2′-*dimethoxydi-α-naphthylmethane*.—A hot solution of 6-bromo-2-methoxynaphthalene (18 g.) in acetic acid (80 c.c.) was treated with a mixture of aqueous formaldehyde (40%; 12 c.c.) and acetic acid (12 c.c.). Sulphuric acid (1 c.c.) was added, and the mixture heated on the steam-bath. The *product* (17 g.) soon separated and after 15 minutes the mixture was cooled and filtered. The residue crystallised from anisole in colourless polyhedra, m. p. 246—248° (Found : Br, 32·3. $C_{23}H_{18}O_2Br_2$ requires Br, 32·9%).

6 : 6′-*Dicyano*-2 : 2′-*dimethoxydi-α-naphthylmethane*.—This was prepared by the usual method from the dibromo-compound (11 g.), cuprous cyanide (5·5 g.), and pyridine (5 c.c.). It (3·6 g.) crystallised from anisole in clusters of needles, m. p. 262—264° to a red liquid (Found : N, 7·3. $C_{25}H_{18}O_2N_2$ requires N, 7·4%).

6 : 6′-*Diamidino*-2 : 2′-*dimethoxydi-α-naphthylmethane*.—This was prepared by the usual method. The *di-isethionate* crystallised from methyl alcohol–acetone in clusters of colourless rods, m. p. 258—261° (Found : N, 8·4. $C_{25}H_{24}O_2N_4,2C_2H_6O_4S$ requires N, 8·4%).

6-*Bromo*-2-*methoxy*-1-*chloromethylnaphthalene*.—Hydrogen chloride was passed into a suspension of trioxymethylene (5 g.) in glacial acetic acid (60 c.c.) until a clear solution was obtained. A solution of

6-bromo-2-methoxynaphthalene (10 g.) in glacial acetic acid (50 c.c.) was then added, and passage of hydrogen chloride continued until crystals started to separate. After 24 hours the product (10·4 g.) was filtered off, washed with ether, and crystallised from light petroleum (b. p. 80—100°). *6-Bromo-2-methoxy-1-chloromethylnaphthalene* separated in colourless needles, m. p. 137—139° (Found: C, 50·6; H, 3·8; total halogen as Br, 56·1. $C_{12}H_{10}OClBr$ requires C, 50·4; H, 3·5; total halogen as Br, 56·0%). When this product was boiled for a few minutes with a little methyl alcohol, it was converted into *6-bromo-2-methoxy-1-methoxymethylnaphthalene*, which crystallised from methyl alcohol or light petroleum (b. p. 80—100°) in colourless plates or needles, m. p. 115—116° (Found: C, 55·2; H, 4·6; Br, 28·3; OMe, 20·5. $C_{13}H_{13}O_2Br$ requires C, 55·5; H, 4·6; Br, 28·5; OMe, 22·1%).

The authors thank Mr. S. Bance, B.Sc., A.R.I.C., for the semi-micro analyses, and the Directors of May & Baker Ltd. for permission to publish these results.

THE RESEARCH LABORATORIES, MAY & BAKER LTD., DAGENHAM.

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63. *The Preparation of Symmetrical Dinitrodiphenyls by the Ullmann Reaction.*

By W. DAVEY and R. W. LATTER.

Symmetrical dinitrodiphenyls have been prepared by the Ullmann reaction, under standard reaction conditions, from pure halogenonitrobenzenes. The results obtained enable a valid comparison of the reactivities of the halogen atoms to be made. The *o*-nitro-group has a greater activating effect on halogen atoms than *p*- or *m*- nitro-groups.

IN a recent comprehensive review of the Ullmann reaction (Fanta, *Chem. Reviews*, 1946, **38**, 139), the reaction conditions for the preparation of symmetrical dinitrodiphenyls and the yields obtained by various workers are incomplete and hence no valid comparison of the reactivities of the halogen atoms in the halogenonitrobenzenes is possible. In the present work standard conditions have been used for the preparation of symmetrical dinitrodiphenyls, and the results therefore enable a true comparison of the reactivities to be made.

Carefully purified halogenonitro-compounds have been converted into diaryls by heating them with freshly precipitated copper in the dry state, and by heating their solutions in nitrobenzene with freshly precipitated copper. In general, the fusion method has given a smoother reaction and a higher yield of the diaryl than the reaction in solution. The results confirm those of previous workers and show that iodo-compounds give the highest yields and the purest products. The activating effect of the nitro-group on halogen atoms is in the order ortho > para > meta, and this is in general agreement with the conclusions of Fanta (*loc. cit.*) for the Ullmann reaction.

EXPERIMENTAL.

(All m. ps. are uncorrected.)

Starting Materials.—Nitroanilines were converted into chloronitro-, bromonitro-, and iodonitro-compounds by the Sandmeyer reaction or by treatment of the diazonium solution with potassium iodide. The crude halogenonitro-compounds were twice distilled in steam, twice crystallised from alcohol, and then dried for several days over phosphoric oxide in a vacuum. Although these compounds distil very slowly in steam, this method has been found the most satisfactory for their purification.

Pure nitrobenzene was prepared by drying A.R. nitrobenzene over potassium hydroxide and then twice distilling it, rejecting the first and the last 20% of the distillate.

Freshly precipitated copper was prepared by gradual addition of A.R. zinc dust to excess of an aqueous solution of A.R. copper sulphate just acidified with sulphuric acid. The precipitate was collected, thoroughly washed with distilled water, alcohol, and finally ether, and dried in a vacuum. The copper was freshly precipitated for each series of reactions, standard conditions being used for the preparation.

Ullmann Reaction by Fusion.—The halogenonitrobenzene (2·5 g.) was placed in a previously dried test tube, embedded in a sand-bath and fitted with a thermometer. The bath was heated to 200° as indicated by the thermometer, and copper powder (1·5 g.) was added in small portions over a period of 20 minutes, the whole being constantly stirred by means of the thermometer. When all the copper powder had been added the temperature was maintained at 200° for a further 10 minutes, raised to 220° and maintained at this temperature for a final 10 minutes, stirring being continued throughout.

After cooling, the tube and contents were crushed and extracted in a Soxhlet apparatus with benzene, care being taken to avoid loss of material during extraction. The bulk of the benzene was removed by distillation, and the remaining benzene and unchanged nitrohalogen compound were removed by exhaustive distillation in steam. The residue was filtered and extracted with hot alcohol. The alcholic solution was then evaporated to dryness in a wide-mouthed flask on a steam-bath. Alcohol, saturated at 0° with the appropriate dinitrodiphenyl, was then added, and the contents of the flask were heated under reflux until solution was complete. The flask was then cooled and maintained at 0° for 1 hour

The crystals which separated were collected rapidly in a pre-cooled funnel, and after being washed with a little saturated alcoholic solution were cooled to 0°, dried in vacuum over phosphoric oxide, and weighed.

When no crystals separated from the alcoholic solution after 1 hour at 0°, the flask was maintained at 0° for a further 30 minutes before the yield was reported as nil.

Ullmann Reaction in Nitrobenzene Solution.—The halogenonitrobenzene (5 g.) was added to copper powder (3 g.) and nitrobenzene (25 g.), and the whole refluxed for 9 hours. After cooling, the contents of the flask were diluted with a little dry benzene and filtered, and the residue was well washed with warm benzene. The benzene–nitrobenzene solution was then exhaustively distilled in steam to remove benzene, nitrobenzene, and unchanged halogenonitro-compound. The residue, after filtration, was dissolved in alcohol and purified as before.

All experiments were carried out in duplicate and repeated using copper-bronze. No marked improvement in yield was obtained by the use of copper-bronze.

The results are summarised in the table together with the reported yields obtained by other workers.

Comparative yields of dinitrodiphenyls.

Nitrohalogen compound.	Yield by fusion (%).	Yield by reaction in nitrobenzene (%).	Yields reported by other workers.	Ref. No.
o-Chloronitrobenzene	40	Nil	52—61	(1)
			52—54 (occasionally 61)	(3)
			60	(2)
o-Bromonitrobenzene	64	45	75	(2)
o-Iodonitrobenzene	65	43	—	(4)
m-Chloronitrobenzene	Nil	Nil	—	—
m-Bromonitrobenzene	15	Nil	—	(4)
m-Iodonitrobenzene	36	Nil	26—52	(5), (6)
p-Chloronitrobenzene	Nil	Nil	—	—
p-Bromonitrobenzene	36	15	—	(7)
p-Iodonitrobenzene	54	25	52	(8)

The references in the last column are used in the discussion which follows.

Discussion.

The yields of *o*-halogenonitro-compounds obtained by the fusion method are somewhat lower than those reported by Fuson and Cleveland (1) (*Org. Synth.*, 1940, **20**, 45), Ullmann (2) (*Ber.*, 1901, **34**, 2174), and Shaw and Turner (3) (*J.*, 1933, 135), but these authors used higher reaction temperatures. The preparation of 2 : 2′-dinitrodiphenyl by this reaction has also been described by Le Fèvre (*J.*, 1929, 733; 1938, 967), Schiemann and Rozelius (4) (*Ber.*, 1932, **65**, 737), and Mascarelli, Longo, and Ravero (*Gazzetta*, 1938, **68**, 33), but none of these workers give any indication of the yield. In the attempted preparation of 2 : 2′-dinitrodiphenyl in nitrobenzene solution a small amount of purple material was produced, but no diphenyl could be isolated, even by chromatographic separation on alumina.

The yields of *m*-halogenonitrobenzenes are in agreement with those obtained by Cumming and Muir (5) (*J. Roy. Tech. Coll., Glasgow*, 1937, **4**, 61). Mascarelli, Longo, and Ravero (6) (*loc. cit.*), Schiemann and Rozelius (*loc. cit.*), and Ullmann and Bielecki (*loc. cit.*) have all described the preparation of 3 : 3′-dinitrodiphenyl but have given no indication of yield.

The yields of 4 : 4′-dinitrodiphenyl agree with those obtained by Ullmann and Bieleki (*loc. cit.*). Mascarelli, Longo, and Ravero (*loc. cit.*) described the preparation of this compound, but gave no indication of the yield.

Acton Technical College,
High Street, Acton, London, W.3.

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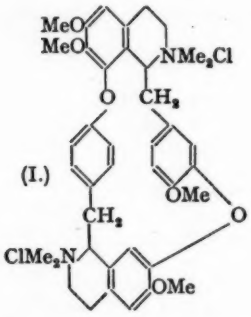
64. *Curare Alkaloids. Part VII. Constitution of* dextro*Tubocurarine Chloride.*

By Harold King.

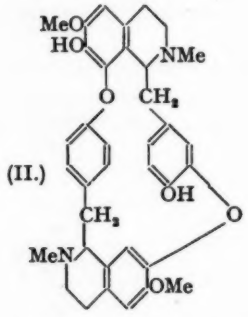
The aim of the present investigation was the determination of the constitution of *dextro*tubocurarine chloride. This has been accomplished by *O*-ethylation followed by a two-stage Hofmann degradation to *O*-ethylbebeerilene, the nitrogen-free substance previously obtained from bebeerine. *dextro*Tubocurarine chloride and bebeerine have therefore the same distribution of methoxy- and phenolic groups, and their particular orientation is known since the structure of bebeerine has previously been completely elucidated.

It was shown in Part I (King, *J.*, 1935, 1381) that *dextro*bebeerine when methylated on its phenolic groups and on its tertiary nitrogen atoms gave a substance, *O*-methylbebeerine methochloride, isomeric with the product obtained by methylation of the phenolic groups of *dextro*tubocurarine chloride. Furthermore, these two completely methylated quaternary alkaloids gave, when submitted to a two-stage Hofmann degradation, one and the same nitrogen-free substance, *O*-methylbebeerilene. The difference between the two completely methylated alkaloids was thus due to diastereoisomerism.

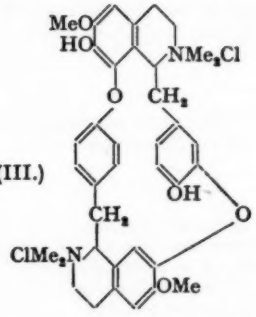
In Part II (King, *J.*, 1936, 1276) the constitution of *O*-methylbebeerine methochloride and *O*-methyltubocurarine chloride was shown to be (I), the difference in these completely methylated



(I.)



(II.)



(III.)

bases residing in the asymmetric centres. In Part IV (King, *J.*, 1939, 1157) it was demonstrated by degradation experiments on *O*-ethylated bebeerine that bebeerine had the constitution (II). It was also pointed out at the same time that the quaternary alkaloid *dextro*tubocurarine chloride might have a similar distribution of phenolic groups.

Through the generosity of the Wellcome Foundation Ltd., who presented me with a supply of the valuable alkaloid, *dextro*tubocurarine chloride, it has been possible to determine the orientation of the phenolic groups in this quaternary salt. On *O*-ethylation it gave amorphous *O*-ethyltubocurarine chloride which when submitted to a two-stage Hofmann degradation gave the nitrogen-free *O*-ethylbebeerilene identical in properties with the substance obtained from bebeerine. *dextro*Tubocurarine chloride must accordingly have the structure (III). The evidence supplied by observations on the optical rotations of the methines obtained from *O*-methylbebeerine methochloride and *O*-methyltubocurarine chloride (Part I, *loc. cit.*) suggests that in *dextro*bebeerine both asymmetric centres are dextrorotatory whilst in *dextro*tubocurarine chloride one is dextro- and one lævo-rotatory.

Experimental.

Anhydrous *dextro*tubocurarine chloride (0·97 g.), absolute alcohol (10 c.c.), 0·5N-alcoholic potash (5·6 c.c.; 2 mols.), and ethyl iodide (1 c.c.) were boiled for 7 hours, a second portion of 0·5N-alcoholic potash (2·8 c.c.) and ethyl iodide (1 c.c.) being added after 3 hours' boiling. The solvents having been removed, water was added and sufficient alcohol to dissolve the precipitated gum, followed by excess of freshly precipitated silver chloride. After thorough mixing by shaking for a few minutes, the solution was filtered and evaporated to dryness. The non-crystalline residue mixed with some sodium chloride was treated with water (20 c.c.) and sodium hydroxide (4 g.), and boiled for 75 minutes. On cooling, the gum was extracted with chloroform, the solvent removed, and the residue boiled with methyl alcohol (10 c.c.) and methyl iodide (2 c.c.) for 8 hours. The solvent having been removed, the residue was dissolved in aqueous alcohol and freed from iodide by addition of silver chloride. The filtered solution was evaporated to dryness, the residue treated with water (20 c.c.) and sodium hydroxide (4 g.), and the solution boiled for 90 minutes. The gum which had separated was taken up in chloroform, the solvent removed, and the residue (0·45 g.) moistened with glacial acetic acid. A crystalline solid rapidly separated (0·14 g.), and on repeated crystallisation from 10 parts of glacial acetic acid retained a melting point of 167—168° and when mixed with authentic *O*-ethylbebeerilene showed no depression of melting point. Both ethers crystallised from acetic acid in sheaves of elongated plates which on drying in the oven at 95° effloresced and lost their transparent appearance. Both when added to concentrated sulphuric acid gave a cherry-red solution (Found: C, 77·0; H, 6·2. Calc. for $C_{38}H_{36}O_6$: C, 77·5; H, 6·2%).

National Institute for Medical Research,
Hampstead, N.W. 3.

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65. *Alumina Catalysts for Vapour-phase Organic Dehydrations, Deaminations, etc.*

By G. Feachem and H. T. S. Swallow.

The publications dealing with the properties of γ-alumina and with the use of alumina catalysts for certain vapour-phase reactions are reviewed. These lead to the conclusions that γ-alumina is the catalytically active species, that purer specimens are more active catalysts, and that active catalysts can be prepared from precipitates that are initially granular: it is not necessary to precipitate gels. Experiments are described that confirm these conclusions, the activities of the catalysts being measured by the rate of dehydration of ethanol to ethylene, under such conditions that the finite rates of diffusion of the reagents in the vapour phase do not seriously affect the rate of the reaction. The effect of crystal size has not been thoroughly studied, but in general, methods of preparation that would be expected to give small crystals give the most active catalysts. The time required to dehydrate boehmite to γ-alumina varies enormously from sample to sample, and care must be used in catalyst testing to ensure that the dehydration is complete: methods for doing this and the difficulties that arise are discussed.

Catalysts made from natural or artificial hydrated aluminas are widely used in the temperature range between about 200° and 400° for organic reactions in the vapour phase that involve amino- and hydroxyl radicals (Sabatier and Reid, " Catalysis in Organic Chemistry ", London, 1923, pp. 690—818). At higher temperatures they are also used for reactions between hydrocarbons, but these processes are not considered here. The reactions considered include hydrations and dehydrations [alcohols to ethers and olefins; ammonium formate to hydrogen cyanide (Johnson, B.P. 220,771)]; deaminations [aniline to diphenylamine (Hill and Hill, B.P. 473,739)]; hydrolyses of arylamines to phenols (Cross, B.P. 584,241); ammonolyses of alcohols to amines, alkylations of primary and secondary to secondary and tertiary amines and many others (Sabatier and Reid, *op. cit.*).

The object of the work described here was to discover which form of alumina was catalytically active and how it should be prepared. Information from the literature indicates that the active species is γ-alumina, and this conclusion is supported by experimental work.

Properties of γ-Alumina.—The name " γ-alumina " is applied to the isometric form of anhydrous alumina, Al_2O_3 (Chatt, *Chem. and Ind.*, 1946, **65**, 78). The only known way of preparing this substance is by dehydration of the orthorhombic (γ) form of the monohydrate, AlO(OH), which is known as boehmite (Biltz and Lemke, *Z. anorg. Chem.*, 1930, **186**, 373; Fricke, *Kolloid Z.*, 1934, **69**, 312; Klever, *Trans. Ceram. Soc.*, 1930, **29**, 149; Rooksby, *ibid.*, 1929, **28**, 399; Weiser and Milligan, *J. Physical Chem.*, 1934, **38**, 1175). This change is reversible (Bentley and Feachem, *J. Soc. Chem. Ind.*, 1945, **64**, 148). Boehmite is prepared by the dehydration of either of the trihydrates bayerite or gibbsite (Fricke; Rooksby; Weiser and Milligan; *locc. cit.*), and also by precipitation of alumina from solution under certain conditions (Biltz, Lehrer, and Meisel, *Z. anorg. Chem.*, 1928, **172**, 292; Boehm, *ibid.*, 1925, **149**, 203; Magarschek, *Leg. Met.*, 1938, No. 2, p. 12; *Chem. Abs.*, 1939, **33**, 2403; Milligan and Weiser, *J. Physical Chem.*, 1936, **40**, 1095; Rooksby, *loc. cit.*; Weiser and Milligan, *Chem. Rev.*, 1939, **25**, 1; Weiser, Milligan, and Purcell, *Ind. Eng. Chem.*, 1940, **32**, 1487; Weiser, Milligan, and Purcell, *ibid.*, 1941, **33**, 669). The conversion of gibbsite into boehmite is reversible, and freshly precipitated boehmite is hydrated on contact with water, becoming first bayerite and then gibbsite (Biltz, Lehrer, and Meisel; Fricke; Weiser and Milligan, 1939; *locc. cit.*). γ-Alumina can be converted (presumably through boehmite) into gibbsite (Bentley and Feachem, *loc. cit.*).

γ-Alumina is not formed from the orthorhombic monohydrate diaspore, which changes into the hexagonal α-alumina (corundum) on heating (Fricke, *loc. cit.*; Laubengayer and Weisz, *J. Amer. Chem. Soc.*, 1943, **65**, 247): this change is reversible (Laubengayer and Weisz, *loc. cit.*). γ-Alumina also changes into corundum on prolonged heating at high temperatures: this change has not, as far as we know, been reversed experimentally.

γ-Alumina is most conveniently recognised by *X*-ray diffraction, and the spacings and intensities of the lines on the powder photograph have been published by many workers and will be found in the A.S.T.M. card index. All the identifications quoted below were obtained in this way, and there is no other established method. If γ-alumina were obtained in large crystals, it could be distinguished from boehmite because the latter would loose water on heating. In practice, however, γ-alumina is always obtained in very small crystals, which adsorb water vapour very strongly. Some adsorptions have been measured on typical specimens of γ-alumina, and these show that this water cannot be driven off by heating in conditions in which boehmite is not decomposed. Below about 200°, boehmite decomposes only very slowly (Bentley and

Feachem, *loc. cit.*), and it is suggested that water adsorbed on γ-alumina might be displaced by a hydrocarbon in an apparatus such as that described by Dean and Stark (*Ind. Eng. Chem.*, 1920, **12**, 486): preliminary experiments showed that some water could be recovered in this way, but the authors were able to obtain *X*-ray powder spectrograms of all their specimens, and this was sufficient, so that investigation was not pursued.

The conversion of boehmite into γ-alumina proceeds reasonably fast at about 400° and it has been observed at temperatures down to 256°, where it was very slow (Bentley and Feachem, *loc. cit.*). Results quoted below show that the rate depends on the previous history of the alumina, and that some specimens of boehmite are only dehydrated very slowly, even at 450°. Any short-period test of catalytic activity is therefore of doubtful validity unless the state of the catalyst is certainly known. The conversion of γ-alumina into corundum usually occurs at about 1200°, but it has been observed down to 800° at atmospheric pressure (Biltz and Lemke, *loc. cit.*; Klever, *loc. cit.*; Parravano and Onorato, *Atti R. Accad. Lincei*, 1929, **10**, 475; *Chem. Abs.*, 1930, **24**, 4681; Rooksby, *loc. cit.*) and at 415° in the presence of a high pressure of steam (Laubengayer and Weisz, *loc. cit.*). The lowest temperature at which this change will occur is not known, but at normal pressures it appears to occur so slowly below about 600° that it is not likely to affect the type of work discussed here.

Alumina Catalysts.—Most of the aluminas described in the literature as dehydration catalysts were made by washing and drying precipitated alumina. The dried solid was then very often heated between about 300° and 500°; *i.e.*, it is likely to have been brought into the γ-condition (Alekseevskii, *J. Russ. Phys. Chem. Soc.*, 1930, **62**, 221,817; *Chem. Abs.*, 1930, **24**, 4442; 1931, **25**, 1138; Alekseevskii and Belotzerkovskii, *J. Gen. Chem. U.S.S.R.*, 1936, **6**, 370, 382; *Chem. Abs.*, 1936, **30**, 5481; Alexander, Horn, and Munro, *Canadian J. Res.*, 1937, **15***B*, 438; *Chem. Abs.*, 1938, **32**, 910; Fricke, Niermann, and Feichtner, *Ber.*, 1937, **70**, 2318; Griessbach and Eisele, U.S.P. 1,775,640; Guichard, *Compt. rend.*, 1934, **198**, 573; Johnson, B.P. 220,771; Mackert, D.R.-P. 486,597, 1926; Patrick, U.S.P. 1,682,241). Other experimenters prepared hydrated forms of alumina, but tested them above about 250° or 300°, so that they were probably converted into γ-alumina during the tests (Alvarado, *J. Amer. Chem. Soc.*, 1928, **50**, 790; Boehringer, D.R.-P. 569,842; *Chem. Abs.*, 1933, **27**, 3788; Burda, *Coke and Chem. U.S.S.R.*, 1932; No. 12, p. 50; *Chem. Abs.*, 1934, **28**, 2321; Spinoglio, *Atti Accad. Padova*, 1935, **51**, 25, *Chem. Abs.*, 1937, **31**, 7733). Taking all these published results together, it seems clear that the species that is catalytically active for dehydrations and related reactions is γ-alumina, and that therefore to obtain an active catalyst it should only be necessary to prepare γ-alumina with a large specific surface. The only method available for this preparation is the dehydration of boehmite, which may be either precipitated directly or obtained by dehydration of either of the trihydrates. The observations of Senderens (*Ann. Chim. Phys.*, 1912, **25**, 449) and of Clark, Graham, and Winter (*J. Amer. Chem. Soc.*, 1925, **47**, 2748) suggest in addition that purification of the alumina will increase its catalytic activity.

There is no reason to suppose that there is any advantage in controlling the conditions of precipitation to produce boehmite directly: the boehmite can equally well be obtained by dehydration of either of the trihydrates. Precipitates of boehmite are usually gelatinous, and so might be expected to have large specific surfaces, but the work of Kearby and Swann (*Ind. Eng. Chem.*, 1940, **32**, 1607) and observations made in this laboratory (Bentley and Feachem, *loc. cit.*) show that the gelatinous form is not necessary: active catalysts can be obtained from granular precipitates. The experiments now to be reported provide further evidence that γ-alumina is the active species and that its activity increases with its purity. They also show that specimens that are likely (from their methods of preparation) to have larger specific surfaces are more active: this point is not conclusively proved, because the exact estimation of crystal sizes (and so of surface areas) from *X*-ray diffraction patterns is too laborious.

Certain precautions are necessary in the dehydration and testing of alumina catalysts. It was observed in preliminary trials that the activity of a catalyst sometimes rises during the first few days of its life, and then settles down to a steady value. There may be several reasons for this: the slow completion of the dehydration to γ-alumina, a change to some other crystalline form by combination with one of the reagents used in the test, or the release of strongly held adsorbed water and the adsorption of other substances. A fall in activity, which would be expected to result from crystal growth or from the formation of corundum, has not been observed in a working catalyst below about 600°. It follows from this that any test lasting for only a few hours may not be reliable, so tests should if possible be continued for long enough to show that the activity is steady.

In addition to this precaution, it is also desirable to complete the dehydration to γ-alumina

before beginning the test, otherwise it will occur during the test and (as the results quoted below show) it may take several days.

If the particular alumina that is being used dehydrates reasonably rapidly at the temperature of the test, then there is no point in dehydrating it at a higher temperature, and so incurring a risk of reducing the active surface by crystal growth. Otherwise the optimum temperature must be found empirically: temperatures of 500° have been used (Fricke, Niermann, and Feichtner, *loc. cit.*; Griessbach and Eisele, U.S.P. 1,775,640; Guichard, *loc. cit.*), and one particular specimen of γ-alumina has been heated to 1000° for an hour without any detectable formation of corundum (Chirnside and Dauncy, B.P. 563,636): this observation has been repeated in this laboratory. It is shown below that the temperature of activation can affect the behaviour of the catalyst, but the effect is small and is not likely to be of much practical importance.

Experimental.

(A) *Apparatus and Method for Catalyst Testing.*—The catalyst activities quoted below were measured with samples of catalyst occupying about 200 c.c. To ensure constant temperature, the catalyst space was surrounded by mercury vapour condensing at atmospheric pressure. The apparatus was arranged to run continuously, day and night, for a week or more with each sample, to ensure that the condition of the catalyst was constant. The reaction was the dehydration of ethanol to ether and ethylene, and under the conditions used, ethylene was the principal product.

The reactant mixture was a solution of ethanol in water, containing 93% of ethanol by weight. This was stored in a reservoir under constant head, and allowed to drip through a fine jet into a short tube of about 4 mm. bore, which was connected by a U-seal of about 2 mm. bore to the evaporating coil. The jet was protected from air-borne solid particles by a sintered-glass filter, and this arrangement made it possible to control the rate of feed down to 20 c.c. per hour. The evaporating coil led into the vapour jacket in which the catalyst tube was situated, so that the reactant solution was slowly warmed and evaporated, and the vapour superheated to approximately the temperature of the catalyst. After passing over the catalyst, the vapour was cooled, first by tap water to about 12°, when most of the water and unreacted ethanol condensed, and then by solid carbon dioxide, when the ether condensed.

The specific gravity of the first condensate was measured, and its difference from unity was regarded as being due to unchanged ethanol. There was never sufficient ether present to form a separate layer and the effect of a little ether on the specific gravity of a dilute ethanol solution is about the same as the effect of an equivalent quantity of ethanol (I.C.T., 1928, **3**, 126). The second condensate was measured and regarded as ether: a guard trap, also cooled by solid carbon dioxide, collected no condensate.

These methods for estimating ether and unchanged ethanol were only approximate: it was not practicable to make accurate analyses, because of the large numbers of tests involved. The errors due to ether in the first condensate and ethanol in the second would tend to compensate each other, and the method would be expected to arrange a series of results in the right order. The results can therefore properly be used to support qualitative conclusions.

The results are expressed either as the pass conversion of the ethanol (the fraction converted into ethylene and ether) or as the pass yield of ethylene (the fraction of the ethanol converted into ethylene), and either of these, usually the latter, is plotted against the feed space velocity (the volume of solution fed to unit volume of the catalyst vessel per hour). The graphs naturally slope down from left to right as the conversion decreases with increasing space velocity, but the curves do not all belong to one family. Some of them cross each other, indicating that the kinetics of the process are different with different catalysts. There is thus no single quantity that can be used to express the activity of a catalyst, and this is best shown as a graph.

Most of the catalysts were tested either as granules passing through a 5/16″ mesh and retained on a 3/16″ mesh or as right circular cylindrical pellets of 3/16″ length and diameter. An approximate calculation was made of the order of magnitude of the differences between the concentrations of the reagents at the solid surface and those in the bulk of the gas phase. For this purpose, the diffusivities were estimated by the method of Gilliland (*Ind. Eng. Chem.*, 1934, **26**, 516). For particles of these small sizes, and for the rates of reaction actually observed, the differences are negligible, so the observed rates can be taken as measures of the activities of the catalysts.

(B) *Time Required for Dehydration of γ-Alumina.*—The following three experiments illustrate the different behaviours of specimens of boehmite of different origins.

(1) *Boehmite from precipitated bayerite.* An alkaline solution of sodium aluminate (65½ kg. of Na_2O, 45 kg. of Al_2O_3, 213½ kg. of water) was added slowly to a stirred solution of 152 kg. of sodium hydrogen carbonate in 1850 kg. of water. The precipitate was washed 41 times with distilled water between 19° and 25°, the ratio of the volume of settled slurry after decantation to the volume after the addition of wash water being 0·7. The slurry was then filtered off, and the cake was dried at 110° and broken into granules, which were sufficiently strong to withstand ordinary laboratory handling. *X*-Ray examination showed that the solid was mainly bayerite, the unstable form of $Al(OH)_3$, containing a little boehmite.

Several specimens of this batch were sieved through 5/16″ on to 3/16″ sieves and heated in air in an electric muffle furnace at 350° for various times: one specimen (denoted by an asterisk in the table) was heated at 460°. The specimens heated at 350° were *X*-rayed, and the phases identified are tabulated below. Some of the specimens were tested for catalytic activity: these are indicated in the table and the activities are shown in Fig. 1. The catalytic activity of the alumina was greatest after it had been heated at 350° for just long enough to convert it all into γ-alumina: further heating caused a small but significant reduction of activity. Heating at 400° gave a catalyst of comparable activity, for which the relation between conversion and space velocity was different from that of any of the catalysts heated at 350°.

Activity tested.	Duration of heating, hrs.	*X*-Ray diagnosis.
—	0	Bayerite and a little boehmite
×	1	Boehmite and a trace of γ-alumina
—	2	γ-Alumina and a little boehmite
×	3½	γ-Alumina and a trace of boehmite
—	4	
—	5	
×	6	Only γ-alumina
—	9	
×	12	
×	24	
×	69 *	Not *X*-rayed

FIG. 1.

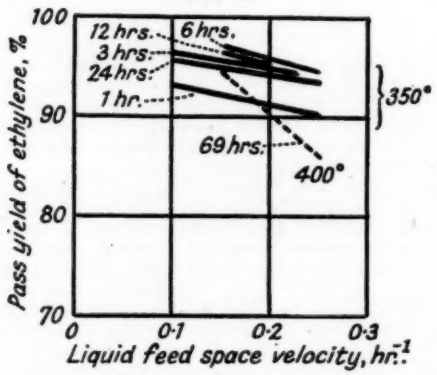


FIG. 2.

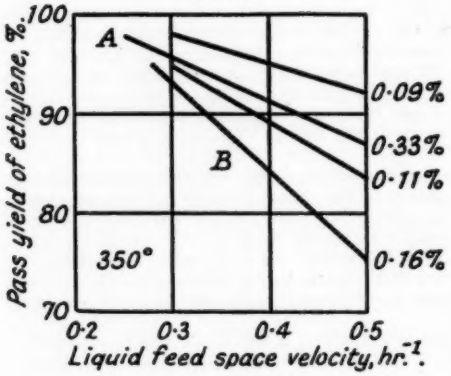


FIG. 3.

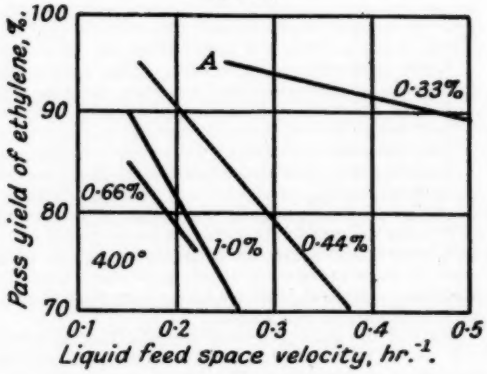


FIG. 4.

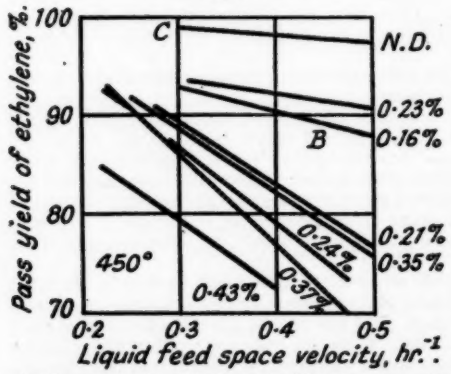
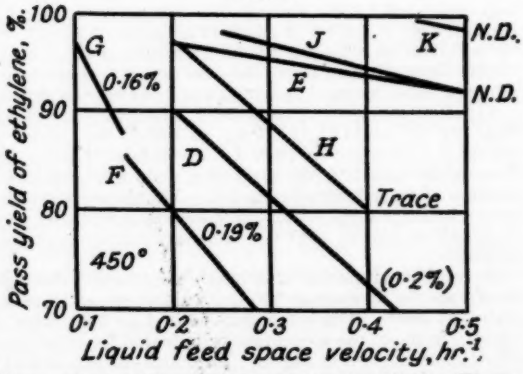


FIG. 5.



The figures against the lines in Figs. 2—5 are the sodium contents of the catalysts, expressed as Na_2O. *Figures in parenthesis are typical of the materials concerned; the remaining figures were determined by analysis ("N.D." means not detected). The temperatures are those at which the catalysts were dehydrated.*

(2) *Boehmite from (purchased) precipitated gibbsite.* Four specimens were taken from two different batches of " Aluminium Hydroxide ", purchased from the British Aluminium Co. Ltd. This material is a crystalline powder of gibbsite, the stable form of $Al(OH)_3$, believed to have been made by slow precipitation in the Bayer process, and therefore likely to be composed of relatively large crystals. These specimens were heated in the electric muffle for various times at various temperatures with the following results :

First batch.		*Second batch.*	
420°, 12 hrs. :	boehmite still present.	400°, 18 hrs. :	boehmite still present.
440°, 6 hrs. :	boehmite not detected.	450°, 12 hrs. :	" " "
490°, 3 hrs. :	trace of boehmite.*	" 18 & 24 hrs. :	trace of boehmite.*
" 6 hrs. :	boehmite not detected.	500°, 1½ hrs. :	" " " *
550°, 1 hr. :	" " "		

* These samples showed the last disappearing traces of the strongest line of the boehmite pattern.

(3) *Boehmite grown under pressure.* Another specimen of this gibbsite was heated in water under pressure at 200° for 60 hours : it was converted into boehmite that was remarkably stable to heat, as follows :

5 days at 360° : only boehmite detected.
8 days at 360° : only boehmite detected.
5 days at 450° (in addition to the 8 days at 360°) : γ-alumina and a small amount of boehmite.

These three sets of results illustrate the very different behaviours on heating of specimens of boehmite of different origins, and also the differences that can occur between batches made apparently by the same method. The ultimate crystal sizes of the boehmite used were not estimated, but qualitatively (from the methods of preparation) the crystal sizes would be expected to be in the same order as the observed times required for dehydration. The activities of catalysts made from gibbsite treated as described in paragraphs (2) and (3) are mentioned in the following section.

(C) *Effect of Purity on Catalytic Activity.*—Bentley and Feachem (*loc. cit.*) recently described a method for preparing an active alumina catalyst from purchased gibbsite by repeated alternate washing (which is accompanied by hydration to boehmite) and dehydration. The increase in activity was attributed to two causes, *viz.*, increasing purity, due to the washing, and decreasing crystal size, due to the repeated changes of phase. In the experiment now to be described the latter cause was absent : several specimens of alumina were precipitated from sodium aluminate and bicarbonate, generally as described in section B(1), but with various concentrations of the reagents, and washed with various degrees of thoroughness. The resulting catalysts were analysed for sodium by the method of Haslam and Beeley (*Analyst*, 1941, **66**, 185). An examination of test results on duplicate samples showed that differences of 0·06% (of the sample) were probably significant, and this figure is taken as the limit of accuracy of the method. The sodium (Na_2O) contents ranged from 1% down to below the above limit, and these are used as an approximate criterion of purity. The specimens were dehydrated at 350°, 400°, and 450° and tested, and their activities are shown in Figs. 2, 3, and 4. The letters *A* and *B* at the left-hand ends of four of the lines identify the same specimens dehydrated at different temperatures : the numbers at the right-hand ends are the sodium contents determined by analysis. In general the purer catalysts are the more active. There is little crossing of the lines for catalysts dehydrated at any one temperature, but if the three graphs are superimposed many of the lines cross each other, again illustrating the change in kinetics caused by a change in the temperature of dehydration.

The line *C* on Fig. 4 shows the activity of a catalyst made by precipitation with ammonia from a solution of aluminium chloride and nitrate. The purest possible reagents were used, and the amounts of sodium and other impurities present in the catalyst were below the limits detectable by analysis.

It is interesting to compare these activities with those of some industrially useful catalysts shown in Fig. 5. Line *D* shows the activity of a catalyst made by dehydrating a commercially available " Activated Alumina " at 450°. The particular batch was not analysed, but a typical value of the sodium content is 0·2% as Na_2O. Before dehydration " Activated Alumina " consists of boehmite, and its crystals are usually small enough to give blurred *X*-ray patterns. The catalytic activity of the dehydrated material can be increased by alternate washing and heating : three such treatments gave line *E* in Fig. 5.

Catalysts made from purchased gibbsite were considerably less active at the same sodium content : this would be expected because they are likely to have been more coarsely crystalline. Lines *F* and *G* on Fig. 5 show the activities of two specimens of boehmite grown under pressure, as described in section B(3). They were made as follows :

	Heated in water at 200° for (hrs.) :	Na_2O, %.	Dehydrated at 450° for (days) :
Line F	16	0·19	5
Line G	60	0·16	3½

In the previous publication (Bentley and Feachem, *loc. cit.*) a pelleted catalyst was described, made by dehydrating purchased gibbsite at 450°. The Na_2O content of the starting material is normally about 0·3%, but the catalytic activity was extremely small (off the scale of Fig. 5). Three cycles of washing and heating raised the activity successively to *H*, *J*, and *K* on Fig. 5, no sodium being detectable after the second treatment.

Discussion.

These results support the conclusion derived from the literature, that γ-alumina is the catalytically active species and that activity is increased by increasing freedom from alkali

impurities and by decreasing crystal size. It is difficult to be certain that in changing either the purity or the crystal size the other is not altered, but the results displayed in Figs. 2, 3, and 4 and the effect of alternate washing and heating on " Activated Alumina " (which is already of small crystal size but not particularly pure), when taken all together, seem to show the effect of increased purity.

The effect of crystal size is less definitely demonstrated, because the crystal sizes were not estimated. But the three catalysts made from gibbsite, which were far less active than their purities would suggest, were made in ways that would be expected to give larger crystals and smaller surface areas. The alternate washing and heating process is likely to break up these crystals and to increase their areas, exactly as alternate oxidation and reduction do with metallic catalysts, and lines *H*, *J*, and *K* on Fig. 5 show how this treatment brings the activity nearer to that of the catalysts precipitated in the laboratory, which are likely to have had smaller crystals initially.

The results illustrate one point of practical importance: to get the greatest activity it is necessary to make γ-alumina, and the times and temperatures required for the dehydration of boehmite to γ-alumina vary greatly from one specimen of boehmite to another. Some of the specimens of boehmite used in this work were dehydrated after 6 hours at 350°, while others needed more than 5 days at 450°. This variation is surprisingly large.

The catalyst activity tests show that the kinetics of the reaction that the catalyst is promoting are changed by a change in the temperature at which the alumina is dehydrated. This is not unexpected, because any heterogeneous catalytic reaction is the result of a series of processes such as adsorption, diffusion in the catalyst and reaction, and this particular reaction—the dehydration of ethanol to ethylene—can go by either of two routes, directly and by the intermediate formation of ether. Alekseevskii (*loc. cit.*, 1930) has observed that the temperature of dehydration of the alumina affects its adsorbing power, low temperatures favouring the adsorption of alcohols and higher temperatures that of olefins. It would not be surprising if this temperature affected the diffusion or the reaction stages in the dehydration of ethanol, as well as the adsorption, and small differences in any of these would alter the balance of the complex system of processes and so alter the observed kinetics.

The authors are indebted to Messrs. C. W. Bunn, H. S. Peiser, J. Haslam, and J. Beeley, and their staffs, for assistance with *X*-ray and chemical analyses, and to Miss W. J. Levy, Miss J. Phillipson, and Messrs. F. J. L. Bentley and S. Ford for assistance in preparing and testing the catalysts.

Imperial Chemical Industries Research Department,
Alkali Division, Northwich, Cheshire. [*Received, March 27th*, 1947.]

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66. *Halogenated Ketones. Part I. The Bromination of Acetone and Methyl Ethyl Ketone.*

By J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones.

Acetone and methyl ethyl ketone have been monobrominated in aqueous solution in the presence of potassium chlorate. By careful fractionation the pure isomeric monobromo-compounds from methyl ethyl ketone have been isolated and characterised and their structures rigidly proved by comparison with synthetic materials prepared by alternative routes. By treatment with aniline under mild conditions the bromo-ketones have been converted into crystalline anilino-ketones which, on boiling with aniline, yield alkylindoles.

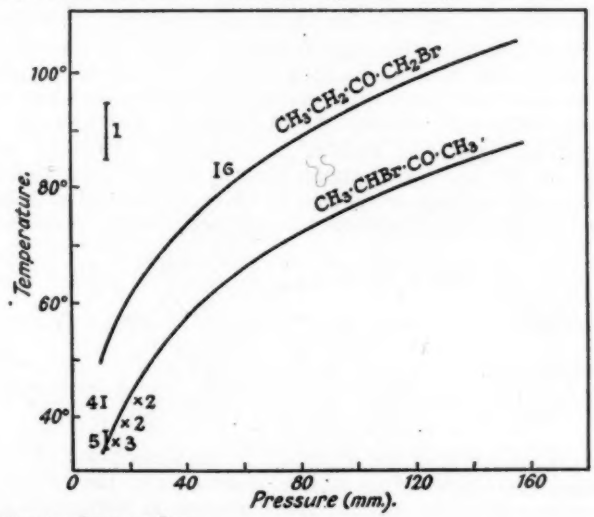
Various methods have been employed for the bromination of aliphatic ketones. Direct treatment with bromine (Sokolowsky, *Ber.*, 1876, **9**, 1687; Emmerling and Wagner, *Annalen*, 1880, **204**, 29; van Reymenant, *Bull. Acad. roy. Belg.*, 1900, 724) gives very impure materials since the liberated hydrogen bromide tends to promote the formation of condensation products. This difficulty is minimised by brominating in the presence of calcium carbonate (Scholl and Matthaiopoulos, *Ber.*, 1896, **29**, 1555; Cherbuliez and Hegar, *Helv. Chim. Acta*, 1932, **15**, 191) or by the use of acetic acid as solvent (Nef, *Annalen*, 1904, **335**, 259; Levene, *Org. Synth.*, 1930, **10**, 12). The most convenient and economical method is undoubtedly that described by Norris (*J. Ind. Eng. Chem.*, 1919, **11**, 828) as having been used in Germany for the manufacture of bromoacetone and brominated methyl ethyl ketone, consisting of bromination in aqueous solution in the presence of potassium chlorate.

$$6CH_3{\cdot}CO{\cdot}CH_3 + 3Br_2 + KClO_3 = 6CH_3{\cdot}CO{\cdot}CH_2Br + KCl + 3H_2O$$

Bromination of acetone under these conditions gave a product which, after fractionation, yielded pure bromoacetone as a colourless liquid with b. p. 63·5—64°/50 mm., $n_D^{18°}$ 1·4697. The freezing point of this material was found to be − 36·5° ± 0·5°, the highest previously recorded having been − 54° (Anon., *Gasschutz und Luftschutz*, 1932, **2**, 264; Stoltzenberg, "Chemische Fabrik," Hamburg, 1930). The latter value probably refers to the crude bromination product, which we found to have a freezing point of − 52° to − 50°. The stability of bromoacetone is notably dependent upon its purity. In the absence of any stabiliser, the crude product appears to keep much better than purified material, but the position is reversed when a trace of magnesium oxide is present. Samples of the crude product were sealed up, both with and without magnesium oxide, both in air and in nitrogen, and were stored in the dark at the ordinary temperature for fifteen months. They had all completely resinified after this time. On the other hand, specimens of the pure bromo-ketone kept over a trace of magnesium oxide, without other precautions, have remained water-white even after six years. It may be noted that the stabilisation of bromo-ketones by the addition of 0·1% or more water is claimed (Commercial Solvents Corp., U.S.P. 2,229,625).

Several studies of the bromination of methyl ethyl ketone have been made in the past, but, as will be seen below and from the figure, it is unlikely that any of the previous workers obtained

Vapour-pressure curves of bromomethyl ethyl and methyl 1-bromoethyl ketones.



Boiling points quoted by previous workers.

$CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2Br$:

(1) *Cherbuliez and Hegar*, loc. cit. (2) *Mohler and Pólya*, Helv. Chim. Acta, 1936, **19**, 1222. (3) *Mohler*, ibid., 1938, **21**, 67. (4) *de Montmollin and Matile*, loc. cit. (6) *Specimen prepared from propionyl bromide and diazomethane* (*Part III*).

$CH_3{\cdot}CHBr{\cdot}CO{\cdot}CH_3$:

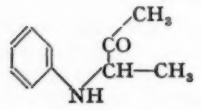
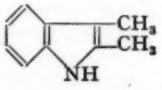
(5) *Cherbuliez and Hegar*, loc. cit.

both of the isomeric monobromo-compounds in a completely pure state. van Reymenant (*loc. cit.*) treated the ketone directly with bromine, de Montmollin and Matile (*Helv. Chim. Acta*, 1924, **7**, 106) claimed to have prepared bromomethyl ethyl ketone by oxidation of bromomethylethylcarbinol, and Cherbuliez and Hegar (*loc. cit.*) brominated the ketone in the presence of water and calcium carbonate. The failure of these workers to obtain the pure isomers is not surprising as their separation is difficult unless efficient fractionating columns are used. With a 25 cm. Widmer column several systematic fractionations, taking about a week to complete, were necessary in order to resolve the mixture of isomers, but with a twenty-plate (CCl_4–C_6H_6) column packed with single-turn glass helices, an almost complete separation of the pure bromo-ketones could be effected in a few hours. Distillation at atmospheric pressure results in considerable decomposition, at water pump pressure the boiling points of the isomers are inconveniently low, and it was found most convenient to operate at 150 mm., using an electrically controlled manostat.

The vapour-pressure curves of the two isomers, which incidentally afford convincing evidence of their individuality, are given in the figure, together with the boiling points reported by previous workers and also that of a sample of bromomethyl ethyl ketone prepared by an alternative route (Part III, this vol., p. 278).

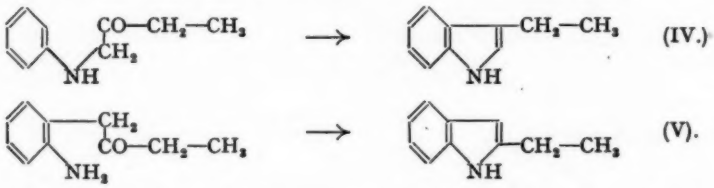
Chemical evidence of the correctness of the structures assigned to these two bromo-ketones has been adduced by treatment with potassium benzoate in alcohol. The resulting keto-benzoates gave crystalline *semicarbazones*, identical with those obtained from substances synthesised by alternative methods.

By treatment with aniline in dilute ethereal solution at the ordinary temperature (the bromomethyl isomer reacts more readily) the bromo-ketones are converted into *methyl 1-anilinoethyl ketone* (I), m. p. 54—55°, and *anilinomethyl ethyl ketone* (III), m. p. 81°. These well-crystallised products are useful for characterisation purposes, but the replacement reactions have to be carried out with care as the anilino-ketones readily cyclise to indoles and tarry by-products are often formed. When methyl 1-anilinoethyl ketone (I) is boiled with aniline

(I.)   (II.)

and aniline hydrobromide for a few minutes, it is converted into 2 : 3-dimethylindole (II), a reaction previously effected by the single-stage treatment of the halogenated ketone with aniline (Vladesco, *Bull. Soc. chim.*, 1891, **6**, 826; Richard, *Compt. rend.*, 1907, **145**, 131).

The question of the mechanism of this type of indole synthesis has been the subject of considerable discussion (*inter alia*, Julian, Meyer, Magnani, and Cole, *J. Amer. Chem. Soc.*, 1945, **67**, 1203; Crowther, Mann, and Purdie, *J.*, 1943, 58; Janetzky, Verkade, and Lieste, *Rec. Trav. chim.*, 1946, **65**, 193 and earlier papers), but in the case cited above no ambiguity can possibly arise. With anilinomethyl ethyl ketone (III) on the other hand, the alternative mechanisms could lead to either 3- or 2-ethylindoles (IV and V respectively), *e.g.*:

(III.)  (IV.)

(V).

Although there is much confusion in the literature in the description of these two substances there is little doubt that the compound (m. p. 46°; *picrate*, m. p. 124°) obtained by treating the anilino-ketone (III) with aniline and aniline hydrobromide is 2-ethylindole. For this isomer m. p.s of 43° and 35° are recorded, but no picrate has hitherto been prepared. The most reliable values for 3-ethylindole would appear to be m. p. 37° [picrate, m. p. 121° (143—144°)] (cf. Robinson and Cornforth, *J.*, 1942, 680).

Experimental.

Bromination of Methyl Ethyl Ketone.—Commercial methyl ethyl ketone was kept overnight over about one-tenth of its weight of anhydrous calcium chloride and then filtered and fractionally distilled. The fraction, b. p. 78·5—80·5°, was collected. Bromine (1600 g.) was added dropwise to a mechanically stirred mixture of the ketone (1240 g.), water (2500 c.c.), and potassium chlorate (300 g.). The temperature of the mixture was at first raised to 50° to initiate the reaction which subsequently proceeded smoothly at 35—40°. After the addition was complete the mixture was allowed to stand for an hour, and the heavy layer of crude material was separated off, shaken with magnesium oxide and water, and dried ($CaCl_2$). The crude product (2250 g.) was practically colourless and remained so in a stoppered bottle left on the bench for 2 months. It could not be fractionally distilled at atmospheric pressure without undergoing considerable decomposition. A portion of this material was roughly distilled to remove small quantities of unchanged ketone and dibromo-ketone, and 425 g. of the isomeric mixture were carefully fractionated as follows. The column contained a packed section, 140 × 1·4 cm., of single-turn 5 mm. diameter glass helices (Fenske), insulated with a 5 cm. thick lagging of magnesia–asbestos. (When tested with carbon tetrachloride–benzene, this column had a theoretical plate value of about 20.) It was fitted with a total condensation partial take-off head, which was operated at a reflux ratio of about 6 : 1. The pressure was controlled at 150 ± 0·5 mm. by an electrically operated manostat. The following fractions were collected (total 409 g.) during an operating period of five hours: (i) b. p. 70—86·5°/150 mm. (7 g.); (ii) b. p. 86·5—87°/150 mm. (245 g.); (iii) b. p. 87—88°/150 mm. (37 g.); (iv) b. p. 88—96°/150 mm. (5 g.); (v) b. p. 96—103°/150 mm. (7 g.); (vi)

b. p. 103—104·5°/150 mm. (10 g.); (vii) b. p. 104·5—105°/150 mm. (98 g.). All the fractions were collected in receivers containing a little magnesium oxide; by this means they did not become discoloured, and samples kept during a period of six years in contact with magnesium oxide have remained practically colourless.

Fractions (ii) and (iii) consisted of methyl 1-bromoethyl ketone, $n_D^{20°}$ 1·4571. The vapour-pressure figures in the accompanying table were obtained by distillation at various pressures, controlled by a manostat.

Fractions (vi) and (vii) consisted of *bromomethyl ethyl ketone*, $n_D^{20°}$ 1·4670 (Found: Br, 52·7. C_4H_7OBr requires Br, 53·0%).

Vapour Pressures of Methyl 1-*Bromoethyl and Bromomethyl Ethyl Ketones.*

Pressure (mm.)	10	20	30	40	50	70	90	110	140	150	760 *
CH_3·CHBr·CO·CH_3 (b. p.)	33°	44°	52°	57·5°	—	70°	75·5°	80°	86·5°	87°	136°
CH_2Br·CO·CH_2·CH_3 (b. p.)	49°	61°	69°	74·5°	79°	87°	92·5°	98°	103·5°	105°	154—5°

* B. p.s. can be measured at 760 mm. if only small quantities are distilled.

Benzoate of Acetylmethylcarbinol (*Benzoate of Acetoin*).—(*a*) Methyl 1-bromoethyl ketone (15·1 g.) and potassium benzoate (16·1 g.) in alcohol (50 c.c.) were heated under reflux for 30 minutes. The alcohol was distilled off, finally under reduced pressure; the benzoyl derivative (15 g.), isolated by means of ether, had b. p. 136—137°/8 mm., $n_D^{19°}$ 1·5082. The *semicarbazone* crystallised from alcohol in plates, m. p. 149° (Found: C, 57·6; H, 6·0; N, 17·1. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·0; N, 16·85%).

(*b*) To a mixture of granulated zinc (100 g.) and sulphuric acid (560 g.; 10%) on the steam-bath, diacetyl (40 g.) was added during 20 minutes with frequent agitation. After a further 15 minutes' heating the product was isolated by continuous ether extraction yielding acetoin (19·3 g.), b. p. 140—142°. Benzoylation was carried out in pyridine with benzoyl chloride, and the product gave the semicarbazone, m. p. 149°, undepressed on admixture with the derivative described under (*a*).

Methyl 1-*Anilinoethyl Ketone*.—A mixture of methyl 1-bromoethyl ketone (6·0 g.) and aniline (5 c.c.) was set aside at 20° for 20 hours. The product, isolated with ether, solidified in a vacuum and after crystallisation from light petroleum (b. p. 60—80°) gave *methyl* 1-*anilinoethyl ketone* (2·5 g.) in blunt needles, m. p. 54—55°. The base is soluble in dilute hydrochloric acid and insoluble in alkalis (Found: N, 8·7. $C_{10}H_{13}ON$ requires N, 8·6%). The *semicarbazone* was obtained from alcohol as a crystalline powder, m. p. 190° (Found: C, 60·4; H, 7·0. $C_{11}H_{16}ON_4$ requires C, 60·0; H, 7·3%).

2 : 3-*Dimethylindole*.—Methyl 1-anilinoethyl ketone (0·25 g.) was heated under reflux with aniline (2 c.c.) containing aniline hydrobromide (0·5 g.) for 15 minutes. On the mixture being poured into dilute hydrochloric acid a crystalline precipitate was obtained, which on crystallisation from light petroleum (b. p. 60—80°) gave 2 : 3-dimethylindole in almost theoretical yield as plates, m. p. 104—105° (*lit.* m. p. 106°).

Benzoate of Propionylcarbinol.—(*a*) Prepared by the method described above from bromomethyl ethyl ketone (7·6 g.), potassium benzoate (8 g.), and alcohol (25 c.c.), the *benzoyl* derivative (7·9 g.) had b. p. 150—152°/8 mm., $n_D^{14°}$ 1·5162 (Found: C, 69·0; H, 6·5. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The *semicarbazone* formed flat needles, m. p. 147°, from alcohol and gave a considerable depression in m. p. on admixture with the isomeric semicarbazone, m. p. 149°, described above (Found: C, 57·6; H, 6·2; N, 16·9. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·0; N, 16·85%).

(*b*) The bromo-ketone prepared by the method described in Part III (*loc. cit.*) was converted into a benzoyl derivative and a semicarbazone identical with those described above.

Anilinomethyl Ethyl Ketone.—To a solution of bromomethyl ethyl ketone (6·05 g.) in ether (10 c.c.) a solution of aniline (5 c.c.) was added with shaking. Aniline hydrobromide began to separate after 5—10 minutes, and after 4 hours the product was isolated with ether. Crystallisation from light petroleum (b. p. 40—60°) yielded *anilinomethyl ethyl ketone* (2 g.) as plates, m. p. 81° (Found: C, 74·3; H, 8·0; N, 8·8. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%). The *semicarbazone* formed clusters of needles from alcohol, m. p. 154° (Found: C, 60·6; H, 7·1. $C_{11}H_{16}ON_4$ requires C, 60·0; H, 7·3%).

2-*Ethylindole*.—Anilinomethyl ethyl ketone (0·45 g.) was heated under reflux with aniline (2 c.c.) and aniline hydrobromide (0·5 g.) for 15 minutes. The product, isolated with ether after the mixture had been poured into dilute hydrochloric acid, had b. p. 150°/14 mm., 105°/0·5 mm. The distillate (almost quantitative yield) solidified on cooling, and after recrystallisation from light petroleum (b. p. 40—60°) formed large plates of 2-ethylindole, m. p. 46° (Verley and Beduwe, *Bull. Soc. chim.*, 1925, **37**, 189, give m. p. 43°; I.C.I. Ltd., Piggott and Rodd, B.P. 330,332 give m. p. 35°). When mixed with an authentic specimen of 3-ethylindole (m. p. 37°), kindly provided by Sir Robert Robinson, P.R.S., a liquid resulted. The *picrate* separated from aqueous alcohol in orange-red needles, m. p. 124°, depressed to 105—108° on admixture with a specimen (m. p. 121—122°) of the picrate of 3-ethylindole (Found: N, 14·7. $C_{16}H_{14}O_7N_4$ requires N, 14·95%).

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67. *Halogenated Ketones. Part II. The Bromination of Methyl Propyl and Methyl* iso*Propyl Ketone.*

By J. R. Catch, D. H. Hey, E. R. H. Jones, and Walter Wilson.

Bromination of methyl propyl ketone in an aqueous medium in the presence of potassium chlorate gave the two expected monobromo-ketones, whereas the *iso*propyl ketone yielded a single product, none of the bromomethyl *iso*propyl ketone being detectable. Bromomethyl propyl ketone readily gave an anilino-derivative, but this could not be cyclised to an alkyl indole; the isomeric 1-bromopropyl ketone, on the other hand, was smoothly converted into a methylethylindole on being heated with aniline and its hydrobromide.

Application of the bromination method described in the preceding paper to methyl propyl ketone gave a mixture of the two isomeric bromo-ketones, *bromomethyl propyl* and *methyl* 1-*bromopropyl ketone*, which were separated by fractional distillation.* The bromination of methyl *iso*propyl ketone has been studied previously by Favorski (*J. pr. Chem.*, 1913, **88**, 658) and by Aston and Greenberg (*J. Amer. Chem. Soc.*, 1940, **62**, 2590, 3135), and methyl 1-bromo*iso*propyl ketone was isolated and characterised, but in neither case was any deliberate attempt made to determine whether any of the isomeric bromo-ketone was produced. The bromination product from this ketone has now been carefully fractionated, and no trace of the bromomethyl *iso*propyl ketone, the properties of which were known as a result of an independent synthesis described in Part III (next paper), could be detected.

The structure of methyl bromopropyl ketone was proved by oxidation with nitric acid, α-bromobutyric acid being obtained in good yield. The bromopropyl ketone was also characterised by interaction with thiourea, a reaction which provides useful confirmation of its structure since the 2-*amino*-4-*methyl*-5-*ethylthiazole* so formed is quite different from the known 2-amino-4-*n*-propylthiazole which would be obtained from the isomeric ketone.

The isomeric bromomethyl ketone smoothly gave *anilinomethyl propyl ketone* on treatment with aniline (identical with the product prepared from the bromo-ketone prepared by the alternative method detailed in Part III), but a few attempts to convert this into either 2- or 3-propylindole by boiling it with aniline in the presence of aniline hydrobromide were unsuccessful. The bromopropyl isomer reacted much more sluggishly with aniline, and the anilino-ketone could not be isolated. Heating with aniline and its hydrobromide, however, converted the bromopropyl ketone into 3-methyl-2-ethylindole, identical with the product obtained by the Fischer reaction from diethyl ketone.

If the structure assigned to the product of the Fischer synthesis is correct [this is by no means certain since it has been shown that alkyl group migrations in the indole series can be brought about by heating with zinc chloride (Crowther, Mann, and Purdie, *J.*, 1943, 58; Verkade and Janetzky, *Rec. Trav. chim.*, 1943, **62**, 763)], the conversion of the methyl bromopropyl ketone into the indole could be regarded as proceeding by a simple cyclisation reaction, in marked contrast to the formation of 2-ethylindole from bromomethyl ethyl ketone (Part I, preceding paper) which apparently proceeds by a different mechanism.

At the time the above work was carried out (1940—42) the main objectives were the preparation and characterisation of the bromo-ketones, and it was not possible to study further examples and to investigate the formation of indoles in greater detail. Sufficient indications have been obtained, however, to show that the further development of this field is not only highly desirable but that it offers distinct possibilities of throwing light on reaction mechanisms at present still obscure, since less complications might be expected to arise from the use of alkyl instead of aryl halogeno-ketones.

Experimental.

Bromination of Methyl n-*Propyl Ketone.*—Commercial methyl *n*-propyl ketone was dried overnight ($CaCl_2$), filtered, and fractionated. The fraction, b. p. 100·5—102°, $n_D^{20°}$ 1·3880, was collected. Bromine (320 g.) was added dropwise to a stirred mixture of the ketone (309 g.), water (240 c.c.), and potassium chlorate (55·2 g.), the reaction vessel bring illuminated throughout by a 60-watt lamp. The reaction was initiated by warming to 55—60°, and once started, it was allowed to proceed at 40—45°. The bromine addition was complete in about 6 hours; the mixture was kept overnight after which the heavy oil was separated, shaken with water and magnesium oxide, and dried ($CaCl_2$). The crude dry product (544 g.), which was practically colourless, was then fractionally distilled. A well-lagged column packed with short lengths of glass tubing was used; the length of the packed portion was about 35 cm. An

* Borrows, Holland, and Kenyon (*J.*, 1946, 1086) describe the bromination of methyl propyl ketone, but their product ($n_D^{20°}$ 1·4629) was probably a mixture of the two isomers.

electrically controlled manostat maintained the pressure at 50 mm. throughout the distillation. Each fraction was collected in a receiver containing a little powdered magnesium oxide. After 6 distillations the following fractions were obtained from 694 g. of crude material: (i) b. p. 70°/50 mm. (14·5 g.); (ii) b. p. 70—76°/50 mm. (5·0 g.); (iii) b. p. 76—78°/50 mm. (93·6 g.); (iv) b. p. 78—80°/50 mm. (173·2 g.); (v) b. p. 80—82°/50 mm. (47·7 g.); (vi) b. p. 82—84°/50 mm. (17·5 g.); (vii) b. p. 84—88°/50 mm. (15·7 g.); (viii) b. p. 88—90°/50 mm. (34·2 g.); (ix) b. p. 90—92°/50 mm. (56·4 g.); (x) b. p. 92—94°/50 mm. (101·7 g.); (xi) b. p. 94—100°/50 mm. (6·3 g.); (xii) b. p. 100°/50 mm. (19·5 g.). Unfortunately the column described in the preceding paper was not available when the above fractionation was carried out; a better separation of the isomers would undoubtedly have been obtained.

Redistillation of fractions (iii), (iv), and (v) (total, 315 g.) gave *methyl* 1-*bromo*-n-*propyl ketone*, b. p. 78·0—78·5°/50 mm., $n_D^{22°}$ 1·4563 (Found: Br, 48·5, 48·5. C_5H_9OBr requires Br, 48·5%). Fractions (viii), (ix), and (x) (total, 192 g.) gave *bromomethyl* n-*propyl ketone*, b. p. 92·0—92·5°/50 mm., $n_D^{23°}$ 1·4620 (Found: Br, 48·8%).

α-Bromobutyric Acid from Methyl 1-*Bromo*-n-*propyl Ketone*.—The bromo-ketone (16·5 g.) was dropped into a mixture of concentrated nitric acid (80 g.) and water (15 c.c.), heated on the steam-bath. After 1 hour the mixture was poured into water, and isolation with ether gave α-bromobutyric acid (10 g.), b. p. 118—120°/25 mm., $n_D^{19°}$ 1·4700 (Michael, *Ber.*, 1901, **34**, 4043 gives b. p. 105—107°/12 mm.). Treatment of the acid chloride with ammonia gave the amide, which crystallised from benzene in needles, m. p. 110° (lit., 112°, 108°, 110—112°).

Anilinomethyl n-*Propyl Ketone*.—Solutions of bromomethyl *n*-propyl ketone (8·3 g.) and aniline (9·3 g.) in dry ether were mixed; after 2 days at 20° the odour of bromo-ketone had almost disappeared. The precipitated aniline hydrobromide was filtered off, and, on evaporation of the ether under reduced pressure, the residue crystallised. The crystals were washed with small quantities of cold methyl alcohol, and crystallisation from the same solvent gave *anilinomethyl* n-*propyl ketone* (6 g.) as plates, m. p. 63—64° (Found: C, 74·6; H, 8·5. $C_{11}H_{15}ON$ requires C, 74·55; H, 8·55%). The anilino-ketone is soluble in dilute hydrochloric acid, from which it is reprecipitated by alkalis.

3-*Methyl*-2-*ethylindole*.—A mixture of methyl 1-bromopropyl ketone (10 g.), freshly distilled aniline (25 c.c.), and aniline hydrobromide (5 g.) was kept at 20° for 1 hour and then refluxed gently for a further hour. The resulting liquid was cooled and poured into a large excess of hydrochloric acid. The crystalline precipitate was washed with dilute ammonia, dried, and distilled, yielding 3-methyl-2-ethylindole (5·5 g.), m. p. 60—62°, b. p. 178°/34 mm., 169—170°/24 mm. The slightly brown product was further purified by steam distillation and then crystallised three times from light petroleum (b. p. 40—60°), in the absence of air, giving the indole in colourless glistening plates, m. p. 65—66° (Found: C, 82·9; H, 8·2. Calc. for $C_{11}H_{13}N$: C, 82·95; H, 8·25%) (Plancher, *Gazzetta*, 1898, **28**, 388, gives m. p. 66°; b. p. 185°/35 mm.). It formed a picrate in methyl alcoholic solution, which, when recrystallised from benzene–light petroleum (b. p. 60—80°) formed brownish-purple needles and had m. p. 150—151° (Plancher, *loc. cit.*, gives m. p. 151°). The m. p. of the indole and of its picrate were not depressed on admixture with authentic specimens prepared by the Fischer reaction from diethyl ketone.

2-*Amino*-4-*methyl*-5-*ethylthiazole*.—A mixture of methyl 1-bromo-*n*-propyl ketone (16·5 g.), thiourea (7·6 g.), alcohol (5 c.c.), and water (5 c.c.) was heated for 3 hours on the steam-bath and then evaporated to dryness under reduced pressure. The base was liberated from the crystalline hydrobromide with alkali, and isolation with ether gave the *aminothiazole* (12 g.), b. p. 147—149°/19 mm., 110°/0·6 mm., $n_D^{20°}$ 1·5625 (Found: C, 50·7; H, 6·9. $C_6H_{10}N_2S$ requires C, 50·65; H, 7·1%). The *picrate*, formed in methyl alcohol, crystallised from acetone in yellow needles, m. p. 239° (decomp.) (Found: C, 38·6; H, 3·7. $C_{12}H_{13}O_7N_5S$ requires C, 38·8; H, 3·5%).

Bromination of Methyl iso*Propyl Ketone* (cf. Favorski, *loc. cit.*; Aston and Greenberg, *loc. cit.*).—The ketone (171 g.; prepared according to Whitmore, Evers, and Rothrock, *Org. Synth.*, Coll. Vol. II, 408) was brominated as described above for the normal ketone. The crude product (278 g.) was fractionated through a column containing a 40 × 1·4 cm. section packed with single-turn glass helices, and working at a reflux ratio of 10 : 1 and 150 mm. the following fractions were collected: (i) b. p. 79° (6·6 g.); (ii) b. p. 79—83° (7·6 g.); (iii) b. p. 83—84° (115·5 g.); (iv) b. p. 84—86° (10·1 g.); (v) b. p. 86—91° (5·2 g.); (vi) b. p. 91—94° (4·6 g.); (vii) b. p. 94—104° (5·8 g.); (viii) b. p. > 100°/35 mm. (18·7 g.) (probably dibromide). Fraction (iii), which had $n_D^{18°}$ 1·4590, was pure methyl 1-bromo*iso*propyl ketone (Found: Br, 48·4. Calc. for C_5H_9OBr: Br, 48·5%). No evidence could be obtained of the presence of any appreciable amount of bromomethyl *iso*propyl ketone, which has b. p. 86°/50 mm., $n_D^{14·8°}$ 1·4467 (Part III; following paper).

Tetrabromopentan-2-*one*.—Bromine (170 g.) was gradually added to methyl propyl ketone (24 g.) with cooling and at such a rate that hydrogen bromide was smoothly and rapidly evolved. After standing overnight the product was heated on a steam-bath for 1 hour and poured into water, and the excess of bromine was removed by passing in sulphur dioxide. The solid product was separated from oil by filtration, and crystallisation from light petroleum (b. p. 40—60°) gave *tetrabromopentan*-2-*one* (80 g.) as glistening plates, m. p. 57—58° (Found: Br, 80·3. $C_5H_8OBr_4$ requires Br, 79·6%).

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68. *Halogenated Ketones. Part III. The Preparation of Bromomethyl Ketones by the Diazomethane Reaction.*

By J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones.

The preparation of eight bromomethyl ketones, by reaction of acyl bromides with diazomethane followed by decomposition of the diazo-ketones with hydrogen bromide, is described.

The direct bromination of unsymmetrical ketones usually gives rise to two isomeric monobromoketones (Parts I and II, preceding papers) which in certain cases can be separated by careful fractional distillation. Since a series of pure bromomethyl alkyl ketones was required for investigation of their physiological properties it seemed desirable to use a preparative method which would yield the pure ketones directly, uncontaminated with any isomers. The diazomethane reaction with acyl halides, originally discovered by Clibbens and Nierenstein (*J.*, 1915, **107**, 1491 and subsequent papers; see also Bradley, Robinson, and Schwarzenbach, *J.*, 1928, 1310, 1545, 2904), was especially suitable for this purpose. The appropriate pure acid bromides were allowed to react with two moles of diazomethane, and the ethereal solutions of the resulting diazo-ketones were then treated with anhydrous hydrogen bromide.

When first prepared these strongly lachrymatory bromomethyl ketones are colourless liquids; they all show a marked tendency to darken and resinify on storage, but this is almost completely inhibited by the presence of a little magnesium oxide.

The ethyl and propyl ketones proved to be identical with those obtained by the direct bromination method (Parts I and II).

Experimental.

The acid bromides were prepared by heating the acid (1 mol.) with phosphorus tribromide (0·5 mol.) for 1·5—2 hours at 150°. They were distilled from the mixture and then redistilled in order to free them from phosphorus compounds and hydrogen bromide.

Diazomethane was obtained in the usual manner by distillation from a mixture of ether, potassium hydroxide solution, and nitrosomethylurea, the latter being prepared in quantity by the very satisfactory method due to Arndt, Loewe, and Avan (*Ber.*, 1940, **73**, 606).

General Method for Bromomethyl Ketones.—The acid bromide (1 mol.) was added slowly to an ice-cold ethereal solution of diazomethane (2 mols.) (dried for at least 3 hours over potassium hydroxide); nitrogen was then evolved and the yellow colour of the diazomethane disappeared rapidly. After 30 minutes at 0°, dry hydrogen bromide was passed in until it was obvious that excess was present; the solution was kept at 0° for a further 30 minutes and then washed with water and sodium hydrogen carbonate solution. The dried ethereal solution was evaporated, and distillation of the residual oil under reduced pressure gave a small first fraction of methyl ester, followed by the bromomethyl ketone.

The properties of the compounds prepared by this method are listed below, all except the first two being new.

Bromomethyl ketone.	Yield, %.	B. p.	n_D.	Found, %.	Req., %.
Ethyl	55	154—155°	1·4670 (20°)	Br, 52·8	Br, 53·0
Propyl	27	92/50 mm.	1·4575 (20)	48·9	48·5
iso*Propyl*	46	86/50 mm.	1·4467 (14·5)	48·9	48·5
n-*Butyl*	50	108/50 mm.	1·4486 (15·5)	45·1	44·7
iso*Butyl*	70	101—102/50 mm.	1·4595 (17)	45·1	44·7
n-*Amyl*	70	96/14 mm.	1·4645 (18)	41·8	41·5
3-*Chloropropyl*	80	114/13 mm.	1·5009 (19·5)	Ag halide, 4·18 mg.	Ag halide, 4·16 mg.
Benzyl	62	106/0·2 mm.	1·5593 (15·5)	Br, 37·2	Br, 37·5

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69. *Halogenated Ketones. Part IV. The Application of the Friedel–Crafts Reaction to the Preparation of Halogenated Aliphatic Ketones.*

By J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones.

By using aluminium chloride as condensing agent and operating in the absence of any solvent other than the acyl halide, a variety of halogenated ketones has been prepared by addition reactions employing ethylene, acetylene, vinyl chloride, and di- and tri-chloroethylene.

ONE of the few applications of the conventional Friedel–Crafts ketone synthesis in the aliphatic series is that involving the condensation of acyl halides with ethylenic and acetylenic compounds. In the simplest case the reaction can be formulated :

$$CH_3{\cdot}COCl + CH_2{:}CH_2 \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2Cl \longrightarrow CH_3{\cdot}CO{\cdot}CH{:}CH_2$$

Although known in principle for a long time (cf. Kondakoff, *Bull. Soc. chim.*, 1892, **7**, 576), in recent years it has been investigated in more detail and extended in its scope.

The earlier investigators (Krapiwin, *Chem. Zentr.*, 1910, I, 1335; Darzens, *Compt. rend.*, 1910, **150**, 707; Norris and Couch, *J. Amer. Chem. Soc.*, 1920, **42**, 2329; Wieland and Bettag, *Ber.*, 1922, **55**, 2246, and Carroll and Smith, *J. Amer. Chem. Soc.*, 1933, **55**, 370), working under the usual Friedel–Crafts conditions and employing inert diluents such as petroleum or carbon disulphide, obtained only poor yields of the halogenated ketones, often together with the vinyl ketones, and in some cases the latter compounds were formed exclusively. Since the halogenated ketones were of particular interest in this present study, it was desirable to obtain them in the best possible yields. In this connection the procedure suggested in certain patents (Schering-Kahlbaum, U.S.P., 1,737,203; I.G. Farbenind., B.P. 459,537) was of interest in that, in the absence of solvents, it was claimed that the β-halogenated ketones were the main product. It has also been claimed (Standard Oil Co., U.S.P., 2,006,198) that the same ketones can be produced, using only catalytic quantities of condensing agents (aluminium chloride, bismuth chloride, etc.), by operating at *ca.* 100° under about 50 atmospheres' pressure.

Only few examples were found in the literature of the employment of halogenated acid halides in such reactions. Carroll and Smith (*loc. cit.*) obtained a very poor yield of chloromethyl 2-chloroethyl ketone by condensation of chloroacetyl chloride with ethylene. Reactions with acetylene, leading to 2-chlorovinyl ketones, have been described by I.G. Farbenind.

$$CH_3{\cdot}COCl + HC{:}CH \longrightarrow CH_2{\cdot}CO{\cdot}CH{:}CHCl$$

(B.P. 461,080) using light petroleum as the solvent together with aluminium chloride (see also Cornillot and Alquier, *Compt. rend.*, 1935, **201**, 837). Kroeger, Sowa, and Nieuwland (*J. Org. Chem.*, 1936, I, 163) preferred to employ stannic chloride in condensations of acid chlorides with mono- and di-substituted acetylenes. The use of vinyl chloride in Friedel–Crafts reactions has been reported by I.G. Farbenind. (U.S.P. 2,137,664), and chlorovinyl ketones were obtained in reactions in light petroleum with aluminium chloride as the condensing agent.

This same condensing agent was employed in all the reactions described in the present paper; the yields obtained were very dependent upon its purity. No solvent was used other than the acyl halide itself, and in a number of instances this was observed to dissolve the aluminium chloride very readily. Vigorous agitation was essential, and in reactions in which, using molar quantities of the reagents, stirring became very difficult, in subsequent experiments the use of an excess of the acyl halide proved advantageous.

In general, the yields obtained with ethylene were better than those with acetylene, much tarry material being formed in the latter case; reactions with vinyl chloride proceeded almost quantitatively, and 1 : 2-dichloroethylene also gave an excellent yield in a condensation with chloroacetyl chloride.

Although it was to be expected that the initial product in reactions between vinyl chloride and acyl chlorides would be a 2 : 2-dichloroethyl ketone, rather than the isomeric 1 : 2-dichloro-

$$CH_3{\cdot}COCl + CH_2{:}CHCl \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}CHCl_2 \longrightarrow CH_3{\cdot}CO{\cdot}CH{:}CHCl$$

ethyl compound, this point had not hitherto been established, probably because of the difficulty of isolating the dichloroethyl ketones, which tend to lose hydrogen chloride spontaneously. In a reaction utilising chloroacetyl chloride, however, it proved fairly easy to isolate the comparatively stable *chloromethyl* 2 : 2-*dichloroethyl ketone*, and this was shown to be different from the 1 : 2-dichloro-isomer prepared by addition of chlorine to chloromethyl vinyl ketone.

EXPERIMENTAL.

Friedel–Crafts Reactions with Olefins and Acetylene. General Method.—The acid chloride (at least 1 mol.) is cooled (ice–salt) and freshly finely-powdered aluminium chloride (1 mol.) is added with stirring. The flask and contents are then weighed and the olefin (or acetylene) passed into the mixture with vigorous stirring at room temperature (cooling is usually necessary) until no further increase in weight is observed. The gain in weight varies from 50 to 100% of the theoretical; only rarely does it approach or attain the theoretical value. The mixture is then poured, with stirring, on crushed ice and extracted thoroughly (best with chloroform), and the extracts are washed, dried (Na_2SO_4), and evaporated. On distillation under reduced pressure of the products from ethylene, etc., varying quantities of the lower-boiling vinyl ketones are usually obtained. The Table lists the substances prepared by this method.

Ketone.	Reagents.	Yield, %.	B. p.	n_D.	Found.	Reqd.
Methyl 2-chloroethyl [1]	$CH_2{:}CH_2$, $CH_3{\cdot}COCl$	40	48°/15 mm.	—	—	—
Chloromethyl 2-chloroethyl [2]	,, $CH_2Cl{\cdot}COCl$	45	81/2·5 mm.	1·4785 (17°)	—	—
Di-(2-chloroethyl) [3]	,, $CH_2Cl{\cdot}CH_2{\cdot}COCl$	30	74/0·8 mm.	1·4726 (18)	Cl, 44·6%	Cl, 45·75%
Bromomethyl 2-chloroethyl	,, $CH_2Br{\cdot}COCl$	65	81/1 mm.	1·5054 (17)	Ag halide, 12·0 mg.	Ag halide, 12·1 mg.
Chloromethyl 2-bromoethyl	,, $CH_2Cl{\cdot}COBr$	35	80/0·4 mm.	1·4960 (14)	Ag halide, 10·9 mg.	Ag halide, 11·3 mg.
Bromomethyl 2-bromoethyl	,, $CH_2Br{\cdot}COBr$	60	77/0·1 mm.	1·5327 (18)	Br, 68·5%	Br, 69·6%
1-*Chloroethyl 2-chloroethyl*	,, $CH_3{\cdot}CHCl{\cdot}COCl$	60	64—65/1·5 mm.	1·4631 (20)	Cl, 44·5%	Cl, 45·75%
1-*Chloroethyl 2-bromoethyl*	,, $CH_3{\cdot}CHCl{\cdot}COBr$	60	78/1 mm.	1·4853 (22)	Ag halide, 10·6 mg.	Ag halide, 10·4 mg.
Chloromethyl 2-chlorovinyl	$CH{:}CH$, $CH_2Cl{\cdot}COCl$	40	71—74/10 mm.	1·5122 (17)	Cl, 53·5%	Cl, 51·1%
Bromomethyl 2-chlorovinyl	,, $CH_2Br{\cdot}COCl$	30	65—68/2 mm.	1·5220 (16·5)	Ag halide, 13·7 mg.	Ag halide, 13·3 mg.
Chloromethyl 2-bromovinyl	,, $CH_2Cl{\cdot}COBr$	40	80/11 mm.	1·5310 (14)	Ag halide, 12·1 mg.	Ag halide, 12·5 mg.
Bromomethyl 2-bromovinyl	,, $CH_2Br{\cdot}COBr$	40	80—85/2·5 mm.	1·5486 (14)	— [6]	—
Methyl 2-chlorovinyl [4]	$CH_2{:}CHCl$, $CH_3{\cdot}COCl$	90	74/100 mm.	1·4649 (18)	—	—
Chloromethyl 2 : 2-*dichloroethyl*	,, $CH_2Cl{\cdot}COCl$	94 [7]	92/1·2 mm. (m. p. 28) [8]	—	Cl, 57·1%	Cl, 60·7%
Chloromethyl 1 : 2 : 2-*trichloroethyl* [5]	$CHCl{:}CHCl$, $CH_2Cl{\cdot}COCl$	75	92—94/3 mm.	1·5123 (18)	Cl, 68·0%	Cl, 67·55%

[1] Excess of acetyl chloride was found desirable in this reaction. [2] Carroll and Smith, *loc. cit.* [3] I.G. Farbenind., B.P. 459,537. [4] Cornillot and Alquier, *loc. cit.*; I.G. Farbenind, B.P. 461,080. This product was isolated by distillation in steam after extraction. [5] See below for experimental procedure. [6] This material could not be analysed since it decomposed very rapidly, almost immediately after distillation. [7] Yield of crystalline product, 60%. [8] Needles from light petroleum (b.p. 40—60°).

The saturated 2-chloroethyl ketones are reasonably stable; samples of the bromomethyl and chloromethyl ketones kept in glass bottles for several months without undue precautions did not undergo any extensive deterioration. Chloromethyl 2 : 2-dichloroethyl ketone did not decompose appreciably at 0°, but, on storage at the ordinary temperature, hydrogen chloride was rapidly evolved leaving a residue of polymeric material.

The 2-halogeno-vinyl ketones polymerise very readily; hydrogen halide is copiously evolved, and the final product is a brittle black solid. Thus methyl 2-chlorovinyl ketone polymerises completely in less than a week, quinol being without effect in inhibiting this polymerisation.

Chloromethyl 1 : 2 : 2-*Trichloroethyl Ketone.*—To a mixture of 1 : 2-dichloroethylene (100 c.c.) and chloroacetyl chloride (22·6 g.), heated under reflux on the steam-bath, powdered aluminium chloride (27 g.) was added with stirring during 1 hour. After a further two hours' heating, the product (see Table) was isolated in the manner described above.

Treatment with semicarbazide acetate in alcohol gave the *semicarbazone* of *chloromethyl* 1 : 2-*dichlorovinyl ketone*, m. p. 142° (Found : N, 18·2. $C_5H_6ON_3Cl_3$ requires N, 18·2%). Hydroxylamine likewise gave the *oxime* of the unsaturated ketone, m. p. 118° (Found : N, 7·25. $C_4H_4ONCl_3$ requires N, 7·45%).

An identical semicarbazone was obtained from the product derived from the tetrachloro-ketone by shaking it with 10% sodium carbonate solution for an hour, distilling (b. p. 70—75°/1 mm.), and treating with semicarbazide acetate.

Chloromethyl Vinyl Ketone.—A mixture of chloromethyl 2-chloroethyl ketone (47 g.) and diethylaniline (50 g.) was kept overnight at the ordinary temperature. It was then diluted with ether, and the ethereal solution was washed thoroughly with dilute hydrochloric acid and dried. The residue obtained on evaporation was distilled under reduced pressure, a little quinol being placed in each receiver. The *vinyl ketone* (17·4 g.; 50%) was obtained as a pale yellow oil with a lachrymatory acrid odour, b. p. 84°/107 mm., 74—75°/57 mm.; $n_D^{20°}$ 1·4708 (Found : Cl, 35·1. C_4H_5OCl requires Cl, 33·9%). In the absence of quinol the ketone polymerises extremely rapidly giving viscous materials which are not depolymerised on redistillation.

When treated with chlorine at − 10°, the ketone gave a slightly impure trichloro-ketone, presumably chloromethyl 1 : 2-dichloroethyl ketone, in 60% yield, b. p. 61°/0·6 mm., $n_D^{13°}$ 1·4981 (Found : Cl, 57·3. $C_4H_5OCl_3$ requires Cl, 60·7%). This could not be induced to crystallise either by cooling or inoculation with the isomeric chloromethyl 2 : 2-dichloroethyl ketone. On warming it with a solution of potassium iodide in acetone, free iodine and a precipitate of potassium chloride were rapidly produced.

Heptachlorobutan-2-one.—Finely powdered aluminium chloride (50 g.) was added to a stirred mixture of trichloroacetyl chloride (60 g.) and trichloroethylene (130 g.) during 30 minutes, after which the mixture was refluxed on the steam-bath for 3 hours with vigorous stirring. The dark solution was poured on ice, and the product was taken up in ether, the ethereal extract being thoroughly washed with sodium hydrogen carbonate solution before being dried and evaporated. Distillation gave two fractions : (i) b. p. *ca.* 80°/1 mm. (6 g.); (ii) b. p. 130—150° (bath temp.)/1 mm., a semi-solid mass. Fraction (ii) was washed with a little cold acetone and crystallised from light petroleum, giving large crystals of *heptachlorobutan-2-one* (12 g.), m. p. 182° (Found : C, 15·2; H, 0·45. C_4HOCl_7 requires C, 15·3; H, 0·32%). The compound has a camphor-like odour and is only slightly irritant to the eyes.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W. 7.

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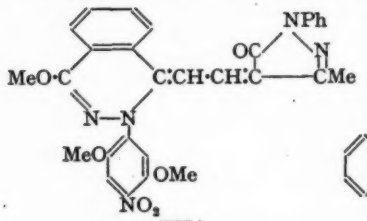
70. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXIII. Phthalazine Derivatives from 4'-Nitro-2' : 5'-dimethoxybenzene-2-naphthol-1-diazosulphonate.*

By (the late) F. M. ROWE, R. L. DESAI, and A. T. PETERS.

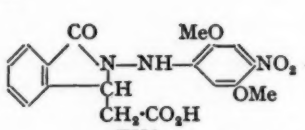
The use of 4-nitro-2 : 5-dimethoxyaniline as diazotisable base in the reactions leading to complex phthalazine derivatives is examined. Whereas 1-hydroxy-3-(4'-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid is readily converted by aqueous sulphuric acid into 4'-nitro-3-phenylphthalaz-1-one, a corresponding reaction with the 4'-nitro-2' : 5'-dimethoxy-derivative (I) follows an unusual course, to give *4'-nitro-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one* (II), also formed from (I) by cold acid dichromate, nitric acid (*d* 1·5) at 50°, or fuming hydrochloric acid in a sealed tube at 140—160°. Compound (II) is isomerised by aqueous hydrochloric acid in a sealed tube at 180° to *4'-nitro-2' : 5'-dimethoxy-3-phenyl-1-methylphthalaz-4-one*. Restricted action of sodium hydroxide on sodium 1-(4'-nitro-2' : 5'-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate, followed by acid hydrolysis, affords compound (I) and 11·6% of 2-(*4'-nitro-2' : 5'-dimethoxyphenylamino*)*isoindolinone-3-acetic acid.*

4'-NITRO-2' : 5'-DIMETHOXYBENZENE-2-NAPHTHOL-1-DIAZOSULPHONATE and aqueous sodium carbonate yielded sodium 1-(4'-nitro-2' : 5'-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate, converted by aqueous sodium hydroxide into *sodium hydrogen* 3-(*4'-nitro-2' : 5'-dimethoxyphenyl*)-3 : 4-*dihydrophthalazine-1-sulphonate-4-acetate*, and thence by boiling dilute hydrochloric acid into 1-*hydroxy*-3-(*4'-nitro-2' : 5'-dimethoxyphenyl*)-3 : 4-*dihydrophthalazine-4-acetic acid* (I). With boiling aqueous sulphuric acid (b. p. 140°) or with fuming hydrochloric

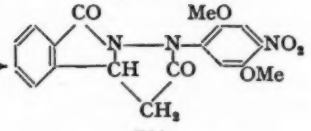
acid (*d* 1·19) in a sealed tube at 140—160°, (I) gave 4′-*nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one* (II). The more normal course of reaction is shown by the action of cold acid dichromate. Methylation of (I) afforded 1-*methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine*, which condensed with 2 : 4-dinitrochlorobenzene or 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone to yield 1-*methoxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine* or -4-(5″-*keto*-1″-*phenyl*-3″-*methylpyrazolinylidene-ethylidene*)-3 : 4-*dihydrophthalazine* (III), respectively.



(III.)



(IV.)



(V.)

The nitro-compound (I) was reduced, best with alkaline hydrosulphite, to the corresponding *amine*, which could not be converted into 4′-*amino*-2′ : 5′-*dimethoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one* by the usual methods. The latter, however, was readily obtained by reducing the corresponding nitro-compound (II) with sodium sulphide; by the action of zinc dust and hydrochloric acid, compound (II) afforded 4′-*amino*-2′ : 5′-*dimethoxy*-N-*phenyl*-3-*methylphthalimidine*. 4′-*Nitro*-2′ : 5′-*dimethoxy*-3-*phenyl*-1-*methylphthalaz*-4-*one* could not be synthesised, but it was formed by isomerisation of compound (II) by heating with aqueous hydrochloric acid (1 : 8) in a sealed tube at 180°.

When sodium 1-(4′-nitro-2′ : 5′-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate was treated with cold aqueous sodium hydroxide for 30 seconds, and the resulting mixed sodium salts were hydrolysed, compound (I) was accompanied by the isomeric 2-(4′-*nitro*-2′ : 5-*dimethoxyphenylamino*)iso*indolinone*-3-*acetic acid*, (IV), the constitution of which was confirmed by boiling it with acetic anhydride, when cyclisation to 2 : 5-*diketo*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)iso*indolinopyrazolidocoline* (V) occurred; reduction with iron and aqueous acetic acid gave the corresponding 4′-*amino*-compound.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford.)

1-*Hydroxy*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (I).—A filtered solution of commercial 50% sodium β-naphthol-1-sulphonate (60 g.) in water (250 c.c.) was stirred slowly at 0° into a solution of diazotised 4-nitro-2 : 5-dimethoxyaniline, prepared in aqueous hydrochloric acid, using 20 g. of base. 4′-Nitro-2′ : 5′-dimethoxybenzene-2-naphthol-1-diazosulphonate separated immediately, and it was collected, washed free from acid with brine, made into a paste with water (200 c.c.), and stirred into 30% aqueous sodium carbonate (150 c.c.); after 15 minutes, a solution of sodium hydroxide (25 g.) in water (120 c.c.) was added and the mixture left at room temperature for 48 hours. *Sodium hydrogen* 3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* was isolated after separation of 4′-nitro-2′ : 5′-dimethoxybenzeneazo-β-naphthol (2·2 g.; 6·2%); it separated from aqueous alcohol as a yellow powder (Found: S, 5·8. $C_{18}H_{16}O_9N_3SNa,H_2O$ requires S, 6·6%), which dyes wool a level orange-brown from an acid bath. The sodium hydrogen salt (25 g.) was boiled with water (500 c.c.), and concentrated hydrochloric acid (60 c.c.) was added gradually until evolution of sulphur dioxide had ceased. The *acid* (I) crystallised from ethyl acetate in small, pale yellow prisms, m. p. 212—213° (14·7 g.; 71·4%) (Found: C, 56·0; H, 4·5; N, 10·85. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·85%).

The *methyl* ester crystallised from methyl alcohol in small, pale yellow needles, m. p. 164° (Found: N, 10·7. $C_{19}H_{19}O_7N_3$ requires N, 10·5%), and the *ethyl* ester formed similar needles from ethyl alcohol, m. p. 152° (Found: C, 58·3; H, 5·1; N, 10·1. $C_{20}H_{21}O_7N_3$ requires C, 57·8; H, 5·1; N, 10·1%); the *acetyl* derivative crystallised from acetic acid in yellow hexagonal plates, m. p. 201—202° (Found: C, 55·7; H, 4·55; N, 9·7. $C_{20}H_{19}O_8N_3$ requires C, 55·9; H, 4·4; N, 9·8%), and the *anilide* crystallised from ethyl acetate in pale yellow needles, m. p. 255° (softens at 249°) (Found: C, 62·4; H, 5·0; N, 12·0. $C_{24}H_{22}O_6N_4$ requires C, 62·3; H, 4·8; N, 12·1%).

1-*Keto*-3-(4′-*nitro*-2′ : 5′-*dimethoxyphenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, prepared as described for the analogous *N*-methyl ethers (*J.*, 1933, 1069), crystallised from aqueous acetic acid in pale yellow needles, m. p. 195° (Found: C, 56·9; H, 4·8; N, 10·3. $C_{19}H_{19}O_7N_3$ requires C, 56·85; H, 4·7; N, 10·5%), soluble in warm aqueous alkalis with a yellow colour.

1-*Hydroxy*-3-(4′-*amino*-2′ : 5′-*dimethoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid*.—Sodium hydrosulphite was added to a solution of the corresponding nitro-compound (20 g.) in water (300 c.c.) and sodium hydroxide (20 g.) at about 70° until the deep red colour became yellow. Hydrochloric acid was carefully added until an almost colourless precipitate had separated completely (excess of acid redissolves

it). Dissolution of the precipitate in hot aqueous sodium carbonate and careful acidification at 70° gave pale yellow prismatic needles, m. p. 193° (decomp.), of the *amine* (10·2 g.; 55·3%) (Found: C, 60·7; H, 5·3; N, 11·5. $C_{18}H_{19}O_5N_3$ requires C, 60·5; H, 5·3; N, 11·8%), which is diazotisable.

4'-Nitro-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one (II).—(*a*) A solution of 1-hydroxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid (20 g.) in concentrated sulphuric acid (100 c.c.) and water (120 c.c.) was boiled for 1·5 hours under reflux. After filtration from some charred material, and dilution of the filtrate (charcoaled) with water, sodium carbonate was added until the mixture was alkaline. The precipitate of *phthalazone* (II) crystallised from alcohol in pale yellow needles, m. p. 254° (softening at 250°) (6·5 g.; 36·8%) (Found: C, 59·9; H, 4·6; N, 12·5. $C_{17}H_{15}O_5N_3$ requires C, 59·8; H, 4·4; N, 12·3%). It is insoluble in sodium carbonate solution, but dissolves in sodium hydroxide solution with an orange colour; salts are formed with mineral acids, *e.g.*, the hydrochloride separated in colourless needles. The *picrate*, prepared in dry alcohol, crystallised from the same solvent in yellow plates, m. p. 229° (Found: N, 14·9. $C_{23}H_{18}O_{12}N_6$ requires N, 14·7%).

(*b*) Compound (I) (7·5 g.) was boiled with concentrated sulphuric acid (50 c.c.) and acetic acid (60 c.c.) for 5 minutes and the mixture poured on ice. Basification with aqueous ammonia (*d* 0·88) gave the above phthalazone, m. p. and mixed m. p. 254° (3·6 g.; 54·5%).

(*c*) A solution of compound (I) (20 g.) in cold concentrated sulphuric acid (200 c.c.) was poured on ice (600 g.), and powdered potassium dichromate (9 g.) was added in small portions during 45 minutes, with continuous vigorous stirring. After being stirred for a total of 5 hours at room temperature, the mixture was basified with aqueous ammonia, when the phthalazone (II) separated (6·6 g.; 37·4%).

(*d*) In nitric acid (*d* 1·5; 50 c.c.) at 50°, compound (I) (10 g.) reacted vigorously; after 2 minutes, the mixture was added to ice and basified; yield, 3·7 g. (43·2%).

(*e*) Compound (I) (2 g.) and fuming hydrochloric acid (*d* 1·19; 15 c.c.) in a sealed tube at 160° for 2 hours gave the above phthalazone in 10% yield.

1-Methoxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-4-methylene-3 : 4-dihydrophthalazine.—4'-Nitro-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one (2 g.) and methyl sulphate (2 g.) were warmed to 60°; after 20 minutes at this temperature, boiling water (100 c.c.) was added and, after the mixture had been allowed to cool, sodium carbonate was added to precipitate the *methylene* base, which crystallised from ethyl acetate in red, prismatic needles, m. p. 131—132° (1·2 g.; 57·7%) (Found: C, 61·0; H, 4·7; N, 11·7. $C_{18}H_{17}O_5N_3$ requires C, 60·8; H, 4·8; N, 11·8%), soluble in dilute mineral acids. 20% Perchloric acid (10 c.c.) was added to 1 g. in aqueous hydrochloric acid; the precipitated *1-methoxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-4-methylphthalazinium perchlorate* crystallised from aqueous acetic acid containing perchloric acid in almost colourless, prismatic needles, m. p. 240° (softens at 233°) (1 g.; 78%) (Found: C, 47·5; H, 4·0; N, 9·3; Cl, 8·0. $C_{18}H_{18}O_9N_3Cl$ requires C, 47·4; H, 4·0; N, 9·2; Cl, 7·8%).

1-Methoxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-4-(2'' : 4''-dinitrobenzylidene)-3 : 4-dihydrophthalazine.—2 : 4-Dinitrochlorobenzene (2 g.) was added to a boiling solution of 1-methoxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-4-methylene-3 : 4-dihydrophthalazine (2 g.) in alcohol (100 c.c.), followed by addition of potassium acetate (3 g.), and the mixture was refluxed for 30 minutes. A deep red colour developed; the *compound*, which separated progressively, crystallised from acetic anhydride in bluish-red prisms, m. p. 230° (2·8 g.; 95·4%) (Found: C, 55·5; H, 3·7; N, 13·6. $C_{24}H_{19}O_9N_5$ requires C, 55·3; H, 3·65; N, 13·4%).

1-Methoxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-4-(5''-keto-1''-phenyl-3''-methylpyrazolinylidene-ethylidene)-3 : 4-dihydrophthalazine (III).—A solution of 1-methoxy-3-(4'-nitro-2' : 5'-dimethoxyphenyl)-4-methylene-3 : 4-dihydrophthalazine (1 g.) and 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone (1 g.) in acetic anhydride (4 c.c.) and acetic acid (6 c.c.) was heated at 100° for 7 hours, and the crystalline product collected next day. The *compound* crystallised from acetic anhydride in brownish-red prisms, m. p. 258° (softens at 240°) (1·3 g.; 85·6%) (Found: N, 12·9. $C_{28}H_{25}O_6N_5$ requires N, 13·0%).

4'-Amino-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one.—A solution of sodium sulphide crystals (8 g.) in water (30 c.c.) was added gradually to a boiling aqueous suspension of 4'-nitro-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one (1 g. in 60 c.c.), during 30 minutes, and the mixture was refluxed for a further hour. After cooling, the *amine* was collected; it crystallised from a mixture of alcohol and ethyl acetate (1 : 2) in small yellow needles, m. p. 260° (0·6 g.; 66%) (Found: C, 65·4; H, 5·5; N, 13·45. $C_{17}H_{17}O_3N_3$ requires C, 65·6; H, 5·5; N, 13·5%).

4'-Amino-2' : 5'-dimethoxy-N-phenyl-3-methylphthalimidine.—A solution of 4'-nitro-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one (5 g.) in concentrated hydrochloric acid (100 c.c.) was boiled, during the addition of zinc dust (10 g.) in small portions, for 1 hour. After being cooled and filtered, the filtrate was made alkaline with sodium hydroxide, and the dry precipitate extracted with alcohol. The *phthalimidine* crystallised from alcohol in small, colourless prisms, m. p. 155—156° (2·1 g.; 45·9%) (Found: C, 68·3; H, 5·8; N, 9·4. $C_{17}H_{15}O_3N_3$ requires C, 68·5; H, 6·0; N, 9·4%), insoluble in aqueous alkalis, but soluble in cold concentrated hydrochloric acid to give a colourless solution; it was diazotisable.

Conversion of 4'-Nitro-2' : 5'-dimethoxy-3-phenyl-4-methylphthalaz-1-one into 4'-Nitro-2' : 5'-dimethoxy-3-phenyl-1-methylphthalaz-4-one.—The 4-methylphthalaz-1-one (2 g.) was heated with aqueous hydrochloric acid (1 : 8; 36 c.c.) at 180° in a sealed tube for 6 hours. The resulting crystals were collected and boiled with dilute hydrochloric acid to remove unchanged material; the residue crystallised from acetic acid in small, pale yellow prisms, m. p. 222° (1·3 g.; 64%) (Found: C, 59·7; H, 4·5; N, 12·5. $C_{17}H_{15}O_5N_3$ requires C, 59·6; H, 4·4; N, 12·3%). The *phthalaz-4-one* is insoluble in boiling dilute mineral acids and aqueous alkalis.

2-(4'-Nitro-2' : 5'-dimethoxyphenylamino)isoindolinone-3-acetic Acid (IV).—A solution of sodium-1-(4'-nitro-2' : 5'-dimethoxybenzeneazo)-β-naphthaquinone-1-sulphonate was prepared from 4-nitro-2 : 5-dimethoxyaniline (20 g.), and a cold solution of sodium hydroxide (25 g.) in water (70 c.c.) was run in, with vigorous stirring. After 30 seconds, the mixture was rendered strongly acid with hydrochloric acid (with the use of a defrothing agent), and was then made alkaline with aqueous sodium carbonate, the insoluble 4'-nitro-2' : 5'-dimethoxybenzeneazo-β-naphthol (7 g.; 19·9%) collected, and the filtrate rendered faintly acid. The whole acid mixture was boiled for 10 hours, the volume being kept constant by adding dilute hydrochloric acid; on cooling, a precipitate (22·4 g.) separated. It was fractionally

crystallised from ethyl acetate; the first crop was 1-hydroxy-3-(4′-nitro-2′ : 5′-dimethoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid, m. p. and mixed m. p. 212—213° (7·5 g.; 19·3%); after the separation of further crops of mixtures, a product, m. p. 221°, was obtained, which on admixture with the above compound, m. p. 212—213°, was depressed in m. p. to 195°. Further purification from ethyl acetate afforded 2-(*4′-nitro-2′ : 5′-dimethoxyphenylamino*)*iso*indolinone-3-*acetic acid* in fine, pale yellow needles, m. p. 221—223° (4·5 g.; 11·6%) (Found: C, 56·3; H, 4·4; N, 10·8. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·85%), soluble in cold aqueous alkalis with an orange-yellow colour. The *methyl* ester crystallised from methyl alcohol in pale yellow prisms, m. p. 146° (Found: N, 10·4. $C_{19}H_{19}O_7N_3$ requires N, 10·5%).

2 : 5-*Diketo*-3-(*4′-nitro-2′ : 5′-dimethoxyphenyl*)iso*indolinopyrazolidocoline* (V).—2-(4′-Nitro-2′ : 5′-dimethoxyphenylamino)*iso*indolinone-3-acetic acid (3 g.) was refluxed with acetic anhydride (14 c.c.) for 15 minutes. The crystals, which separated on cooling, recrystallised from ethyl acetate in pale yellow prisms, m. p. 208° (2·4 g.; 84%) (Found: C, 58·6; H, 4·4; N, 11·6. $C_{18}H_{15}O_6N_3$ requires C, 58·5; H, 4·1; N, 11·4%), of the *anhydro*-derivative (V), insoluble in aqueous alkalis.

2 : 5-*Diketo*-3-(*4′-amino-2′ : 5′-dimethoxyphenyl*)iso*indolinopyrazolidocoline*.—The above nitro-compound (2 g.) was dissolved in acetic acid (30 c.c.) and water (30 c.c.), and iron powder (4 g.) was added gradually during 10 minutes. The mixture was filtered (charcoal), diluted with water, and partly neutralised; the *amine* then separated (1·1 g.; 70·7%); it crystallised from ethyl acetate in brownish-grey prisms, m. p. 174° (Found: C, 63·6; H, 5·4; N, 12·4. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0; N, 12·4%), soluble in dilute mineral acids and diazotisable. The *acetyl* derivative separated from acetic anhydride in colourless prisms, m. p. 259° (Found: N, 10·7. $C_{20}H_{19}O_5N_3$ requires N, 11·0%).

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Clothworkers' Research Laboratory,
The University, Leeds. [*Received, April 16th*, 1947.]

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71. *Reactions of Unsaturated Compounds. Part V. The Action of Organic Peracids on β-Diisobutylene (2 : 4 : 4-Trimethylpent-2-ene).*

By A. Byers and W. J. Hickinbottom.

β-Di*iso*butylene (2 : 4 : 4-trimethylpent-2-ene) reacts with perbenzoic, peracetic, and performic acids to give smaller or larger amounts of an unsaturated alcohol in addition to the normal product.

With perbenzoic acid in chloroform solution, the main product is 2 : 3-*epoxy*-2 : 4 : 4-*trimethylpentane*; the yield of unsaturated *alcohol* is small.

An acetic acid solution of peracetic acid reacts to yield, after alkaline hydrolysis, 2 : 4 : 4-*trimethylpentane*-2 : 3-*diol* and 2 : 4 : 4-*trimethylpent*-1-*en*-3-*ol* in approximately equal amounts. A third product is an apparently homogeneous oil, b. p. 145—151°/25 mm., having the molecular formula $C_{16}H_{32}O_3$. It yields at least two isomeric crystalline *mono*-p-*nitrobenzoates* and by acid hydrolysis is split into C_8 residues. These reactions suggest that the oil is a mixture of isomeric monohydroxy-compounds, each containing two ether linkages. Probable structures are discussed.

Performic acid in excess of formic acid reacts with β-di*iso*butylene in a similar manner, except that the yield of glycol is considerably greater. There is evidence also of the formation of a diether of the formula $C_{16}H_{32}O_2$.

Perbenzoic acid is a recognised reagent for the preparation of epoxides directly from olefins (Prileschajew, *Ber.*, 1909, **42**, 4811; *J. Russ. Phys. Chem. Soc.*, 1911, **42**, 1387; Böeseken and Blumberger, *Rec. Trav. chim.*, 1925, **44**, 90; Nametkin and Brüssoff, *J. pr. Chem.*, 1926, **112**, 169; Meerwein, *ibid.*, 1926, **113**, 9). There appears to be no well-authenticated example of this reaction proceeding other than with the formation of the epoxide, although Meerwein (*loc. cit.*) has reported an abnormal consumption by unsymmetrically substituted olefins. No abnormal products were isolated or identified. Bradsher (*J. Amer. Chem. Soc.*, 1944, **66**, 45), however, has described a dioxide $C_{20}H_{16}O_2$ from 1 : 1 : 2-triphenylethylene, but its structure is still uncertain.

In the present paper it is found that perbenzoic acid reacts with β-di*iso*butylene (2 : 4 : 4-trimethylpent-2-ene) (I) to form the corresponding epoxide (II). The product, however, is not homogeneous; there is a noticeable amount of a compound isomeric with the epoxide, but differing from it in boiling point and refractive index, and also in being unsaturated. It yields an *α-naphthylurethane* and a p-*nitrobenzoate* which have been found to be identical with those from the unsaturated alcohol obtained by the action of peracetic acid on β-di*iso*butylene.

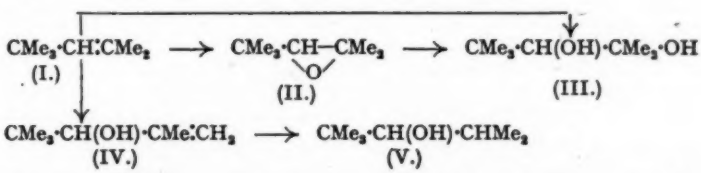
Peracetic acid in ethereal solution is reported to react with olefins to give the epoxide as the primary product (Arbusov and Michailov, *J. pr. Chem.*, 1927, **127**, 1, 92). If acetic acid is used as a solvent, the epoxide ring may be opened with the formation of a glycol and its esters (Böeseken *et al.*, *Rec. Trav. chim.*, 1926, **45**, 838; 1928, **47**, 683; 1929, **48**, 363; 1935, **54**, 657;

Arbusov and Michailov, *loc. cit.*). Some olefins are reported to behave abnormally in that poor yields of the glycol are obtained, together with resinous matter and other unidentified products (Böeseken and Elsen, *Rec. Trav. chim.*, 1929, **48**, 363; Arbusov and Michailov, *loc. cit.*). As far as the authors are aware, there is no record of any of the products of this reaction having been isolated, or of any reliable indication of their nature.

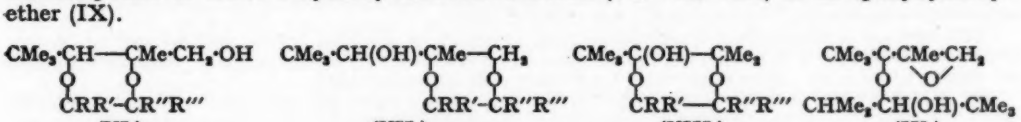
In the present paper, a study has been made of the behaviour of β-di*iso*butylene towards peracetic acid in acetic acid solution. Reaction occurs exothermally, and the product, after alkaline hydrolysis, contains not only the expected glycol but important amounts of an unsaturated alcohol (*A*) and a higher-boiling viscous oil (*B*). The yields of these three main products vary somewhat with the experimental conditions, but in general the glycol and the unsaturated alcohol are formed in approximately equal amounts (see p. 288); the yield of the oil (*B*) is generally somewhat lower.

The glycol is presumably identical with that isolated by Prileschajew (*Ber.*, 1909, **42**, 4811) from the hydrolysis of the mixed epoxides from a mixture of α- and β-di*iso*butylenes. It is now identified as **2 : 4 : 4-*trimethylpentane*-2 : 3-*diol*** (III) by oxidative fission to trimethylacetaldehyde, and by its independent preparation by oxidising β-di*iso*butylene with *tert.*-butyl hydrogen peroxide and osmium tetroxide. It was also obtained by hydrolysis of 2 : 3-epoxy-2 : 4 : 4-trimethylpentane (II).

The unsaturated alcohol (*A*) has the molecular formula $C_8H_{16}O$ and was purified through its crystalline p-***nitrobenzoate***. It was further characterised by its **3 : 5-*dinitrobenzoate*** and its ***α-naphthylurethane***. The unsaturated character of the alcohol was demonstrated by reaction with perbenzoic acid and hydrogenation to 2 : 4 : 4-trimethylpentan-3-ol (V). This identifies the unsaturated alcohol unambiguously as **2 : 4 : 4-*trimethylpent*-1-*en*-3-ol** (IV). The formation of this alcohol from β-di*iso*butylene occurs with alteration in the position of the double bond. The mechanism of this reaction forms the subject of another paper.



The higher-boiling fraction (*B*) is an apparently homogeneous viscous oil, b. p. 145—151°/25 mm., of the molecular formula $C_{16}H_{32}O_3$. It reacts with *p*-nitrobenzoyl chloride in pyridine to yield a mixture of crystalline *p*-nitrobenzoates and a viscid oil. One ester has been obtained pure and is a ***mono*-p-*nitrobenzoate***, $C_{16}H_{31}O_2(CO_2{\cdot}C_6H_4{\cdot}NO_2)$. The lower-melting fractions of the ester have the same composition. It is evident that fraction (*B*) consists of at least two isomers, each containing one free hydroxyl group. Evidence of the nature of one of the other oxygen atoms is provided by its hydrolysis with aqueous alcoholic sulphuric acid in presence of 2 : 4-dinitrophenylhydrazine. A ***dihydropyrazole***, $C_{14}H_{18}O_4N_4$, is formed identical with that from 1 : 2-epoxy-2 : 4 : 4-trimethylpentan-3-ol, showing that fission has occurred to a C_8 residue. The simplest and also the most probable explanation of this observation is that the compound $C_{16}H_{32}O_3$ is an ether in which two C_8 residues are joined together by at least one oxygen. In arriving at this conclusion due consideration has been given to the possibility that $C_{16}H_{32}O_3$ has a tetra*iso*butylene structure, which may also break down under the influence of fairly concentrated acid. But it seems likely that the degradation of such a structure would not yield such simple products as have been obtained. Moreover the tetra*iso*butylene structure does not fit in well with some more recent and unpublished observations on analogous products. If the compound $C_{16}H_{32}O_3$ is then formulated as $HO{\cdot}C_8H_{15}{\cdot}O{\cdot}C_8H_{16}O$, the disposition of the third oxygen as a second ether linkage is indicated. This leads to the formulation of the compound as either a hydroxy-substituted dioxan (VI, VII, VIII) or an epoxyhydroxy-ether (IX).



(R, R′, R″, R‴ = CMe_3, Me, H.)

Of these, the dioxan structure is considered to be the more probable.

The use of performic acid for the hydroxylation of olefins has recently been developed by Swern, Billen, Findley, and Scanlan (*J. Amer. Chem. Soc.*, 1945, **67**, 1786), and Swern, Billen, and Scanlan (*ibid.*, 1946, **68**, 1504). In this procedure, the performic acid is prepared in presence of the olefin by adding hydrogen peroxide (30%) to a solution of the olefin in anhydrous formic acid. The authors claim that no products other than the monoformic ester of the glycol are obtained. It is found that β-di*iso*butylene reacts with hydrogen peroxide in formic acid to yield a product which after alkaline hydrolysis does consist largely of the expected glycol. There is formed in addition 2 : 4 : 4-trimethylpent-1-en-3-ol and higher boiling material, which is presumably substituted dioxan. The yield of these by-products is much smaller than that from peracetic acid, but if the observations of Swern *et al.* are to be accepted, β-di*iso*butylene is an exception among other olefins in yielding by-products when acted upon by performic acid.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. B. ps. are uncorrected unless the contrary is stated.)

β-Di*iso*butylene (2 : 4 : 4-trimethylpent-2-ene) was obtained from Imperial Chemical Industries Ltd. (Billingham Division), and was substantially pure, b. p. 104·1°/748 mm. (corr.), $n_D^{20°}$ 1·4160. The position of the double bond was confirmed by ozonolysis to trimethylacetaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 208°; semicarbazone, m. p. and mixed m. p. 190°).

Oxidation by *tert.*-butyl hydrogen peroxide in *tert.*-butyl alcohol with osmium tetroxide as catalyst (Milas and Sussman, *J. Amer. Chem. Soc.*, 1936, **58**, 1302) gave trimethylacetaldehyde and 2 : 4 : 4-*trimethylpentane*-2 : 3-*diol*, prismatic needles from light petroleum (b. p. 40—60°), m. p. 65—66° (Found : C, 65·6; H, 12·3. $C_8H_{18}O_2$ requires C, 65·7; H, 12·5%).

Reaction with *p*-nitrobenzoyl chloride in pyridine yielded an ester, forming stellate groups of needles from light petroleum (b. p. 40—60°), m. p. 77—78°, which was probably the *mononitrobenzoate* (Found : C, 60·5; H, 7·2. $C_{15}H_{21}O_5N$ requires C, 61·0; H, 7·1%).

Oxidation of the glycol by lead tetra-acetate in acetic acid or by aqueous-alcoholic periodic acid gave trimethylacetaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 208°; semicarbazone, m. p. and mixed m. p. 190°).

2 : 4 : 4-Trimethylpentane-2 : 3-diol on being heated with 2 : 4-dinitrophenylhydrazine in 50% aqueous-alcoholic sulphuric acid presumably underwent a pinacolin rearrangement to give the 2 : 2 : 3 : 3-*tetramethylbutanal* 2 : 4-*dinitrophenylhydrazone*, golden yellow felted needles from alcohol–pyridine, m. p. 163—164° (Found : C, 54·7; H, 6·5; N, 17·9. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5; N, 18·2%).

Reaction of β-Diisobutylene with Perbenzoic Acid.—Freshly distilled β-di*iso*butylene (50 c.c.) and a dry chloroform solution of perbenzoic acid (30 g.) were mixed and kept at room temperature in the dark until all the peracid had disappeared. The solution was then shaken successively with aqueous sodium carbonate and water, before being dried and distilled. 2 : 3-*Epoxy*-2 : 4 : 4-*trimethylpentane* (26·4 g.) was collected in an approximately pure state between 120° and 135°, $n_D^{20°}$ 1·4117, with a small amount of a fraction (1·15 g.) at 150—160°, $n_D^{20°}$ 1·4350. The pure epoxide boils at 130—131° (corr.), $n_D^{20°}$ 1·4092 (Found : C, 74·7; H, 12·5. $C_8H_{16}O$ requires C, 74·9; H, 12·6%); it is a clear mobile liquid with an odour reminiscent of the parent olefin, and is stable to N/100-aqueous permanganate over a period of at least 2 hours. It is very slowly hydrolysed by cold water, somewhat more rapidly by boiling with water or by cold dilute sulphuric acid, to yield 2 : 4 : 4-trimethylpentane-2 : 3-diol.

The fraction, b. p. 150—160°, was unsaturated and reacted with α-naphthyl *iso*cyanate to yield, among other products, the α-naphthylurethane of an unsaturated alcohol, identical with that derived from the reaction of peracetic acid. The identity was confirmed by the preparation of the *p*-nitrobenzoate and its comparison with an authentic specimen.

The unsaturated alcohol isolated in an approximately pure state was less than 1% of the total oxidation product.

Reaction of β-Diisobutylene with Peracetic Acid.—(a) *Preparation of peracetic acid.* An approximately M-solution of peracetic acid was prepared by adding 450 c.c. of acetic anhydride containing 4·5 g. of sulphuric acid to 90 c.c. of commercial 30% hydrogen peroxide. Efficient stirring and a cooling bath are both necessary, as well as a controlled addition of the acetic anhydride, in order to maintain a temperature of 20—25° in the mixture. About 4—5 hours are required for the addition, and after a further period of 1 hour only small amounts of hydrogen peroxide were present. In the work described in this paper, the solution was kept for at least 12 hours until all the hydrogen peroxide had disappeared. The solution then contained approximately 60—65 g. of peracetic acid as determined by Smit's method (*Rec. Trav. chim.*, 1930, **49**, 675). It was used for the oxidations described in this paper, either (i) as prepared and containing free sulphuric acid, or (ii) after being stirred with 10 g. of finely powdered anhydrous sodium acetate to remove the free mineral acid.

This method of preparation is essentially that described by Findley, Swern, and Scanlan (*J. Amer. Chem. Soc.*, 1945, **67**, 412), which is a modification of Smit's method (*loc. cit.*, p. 691). A temperature of 40° during the reaction, as recommended by Findley *et al.*, is unnecessary.

(b) *Reaction with peracetic acid.* The following general conditions were used. Freshly distilled olefin (1·1 mols.) was added slowly to the solution of the peracid (1 mol.). Reaction occurs exothermally, and efficient cooling and stirring are necessary to maintain a temperature of 20—30° during the addition. The mixture was kept overnight or until all the peracid had gone; it was then neutralised by adding a solution of 400 g. of sodium hydroxide in 800 c.c. of water. An oil separated and was stirred with the alkaline solution until neutral.

The upper layer was then removed and combined with the etheral extracts of the lower alkaline layer. After removal of the volatile solvent, the product was heated under reflux for 2—3 hours with a solution of 50 g. of potassium hydroxide in 100 c.c. of 50% aqueous methyl alcohol to hydrolyse any esters which might have been present. The product was isolated by dilution with water and extraction with ether. The dried ethereal extract was freed from solvent, and the residue distilled under reduced pressure. This preliminary distillation gave three main fractions: (*A*) b. p. <90°/30 mm., (*B*) b. p. 90—120°/30 mm., (*C*) b. p. 130—150°/30 mm.

(c) *Identification of the products.* The fraction (*A*) was distilled through a short column packed with glass helices. The following gives a typical separation, any unchanged olefin being neglected: 130—145°, 1·10 g., $n_D^{20°}$ 1·4115; 145—150°, 2·4 g., $n_D^{20°}$ 1·4242; 150—160°, 9·4 g., $n_D^{20°}$ 1·4334; 160—175°, 3·3 g., $n_D^{20°}$ 1·4363; 175—185°, 1·3 g., $n_D^{20°}$ 1·4353; the residue (2·25 g.) solidified on cooling and consisted chiefly of 2 : 4 : 4-trimethylpentane-2 : 3-diol. Further fractionation concentrated the greater part of the product in the fraction 150—160°, with smaller amounts at 130—145° and 170—180°.

(d) *Isolation of* 2 : 4 : 4-*trimethylpent*-1-*en*-3-*ol*. Preliminary examination showed that the fraction b. p. 150—160° was unsaturated and was essentially an alcohol. It was converted, by reaction with *p*-nitrobenzoyl chloride in pyridine, into a crystalline p-*nitrobenzoate*, very pale yellow plates from alcohol, m. p. 79—80° (Found: C, 64·75; H, 6·85; N, 5·2. $C_{15}H_{19}O_4N$ requires C, 64·95; H, 6·9; N, 5·05%).

Hydrolysis of the pure *p*-nitrobenzoate with aqueous-alcoholic alkali gave pure 2 : 4 : 4-*trimethylpent*-1-*en*-3-*ol*, b. p. 154·8—155·0° (corr.)/753 mm., $n_D^{20°}$ 1·4372 (Found: C, 74·7, 74·6; H, 12·65, 12·55. $C_8H_{16}O$ requires C, 74·9; H, 12·6%).

It was characterised by its 3 : 5-*dinitrobenzoate*, platelets from alcohol, m. p. 123° (Found: C, 55·8; H, 5·8; N, 8·9. $C_{15}H_{18}O_6N_2$ requires C, 55·7; H, 5·9; N, 8·7%), and its α-*naphthylurethane*, needles from light petroleum (b. p. 60—80°), m. p. 137° (Found: C, 76·6; H, 7·7. $C_{19}H_{23}O_2N$ requires C, 76·7; H, 7·8%).

Hydrogenation of the unsaturated alcohol in absolute alcohol (PtO_2) gave 2 : 4 : 4-trimethylpentan-3-ol, b. p. 151—152° (corr.), $n_D^{20°}$ 1·4287; α-*naphthylurethane*, spherical aggregates of small needles from light petroleum (b. p. 60—80°), m. p. 110° alone or admixed with a genuine specimen (Found: C, 76·7; H, 7·8. $C_{19}H_{25}O_2N$ requires C, 76·3; H, 7·7%). The identification was further confirmed by oxidation of the reduced alcohol to pentamethylacetone; 2 : 4-*dinitrophenylhydrazone*, orange-red laminæ, m. p. and mixed m. p. 163—164° (Found: C, 54·55; H, 6·4; N, 18·2. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5; N, 18·2%).

(e) *Identification of* 1 : 2-*epoxy*-2 : 4 : 4-*trimethylpentan*-3-*ol*. The fraction b. p. 175—185°, after further distillations, gave a colourless oil, b. p. 180—185°, which was only approximately pure. An alcoholic solution reacted with a hot solution of 2 : 4-dinitrophenylhydrazine in 50% sulphuric acid to give bright red needles from glacial acetic acid, m. p. 204°.

For comparison, 1 : 2-*epoxytrimethylpentan*-3-*ol* was prepared by interaction of 2 : 4 : 4-trimethylpent-en-3-ol and perbenzoic acid in chloroform. After the usual treatment to remove free acid and excess of solvent, the approximately pure epoxide was collected at 80—83/25 mm. as a colourless oil, $n_D^{20°}$ 1·4407, which solidified on cooling, m. p. 28—29° after draining on porous earthenware (Found: C, 67·1; H, 11·4. $C_8H_{16}O_2$ requires C, 66·7; H, 11·2%). It reacted with 2 : 4-dinitrophenylhydrazine to yield a *compound*, m. p. 204°, identical with that obtained as previously described (Found: C, 55·0; H, 6·0; N, 18·1. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%). This compound is probably a 2 : 4-*dinitrophenylpyrazoline* having methyl and *tert.*-butyl substituents, the orientation of which is uncertain owing to the possibility of isomerisation during the preparation.

(f) *Isolation of* 2 : 4 : 4-*Trimethylpentane*-2 : 3-*diol*. The fraction (*B*) (see above), b. p. 90—120°/30 mm., solidified on cooling, and by draining and crystallisation from light petroleum (b. p. 40—60°) the pure glycol was obtained, m. p. and mixed m. p. 65—66°.

(g) *Isolation of a monohydroxy-diether*. The high-boiling fraction (*C*) was distilled under reduced pressure after a further hydrolysis. The following is a typical preliminary separation: 100—120°/27 mm., 1·8 g., $n_D^{20°}$ 1·4452 (deposited glycol on cooling); 120—135°/26 mm., 0·5 g., $n_D^{20°}$ 1·4465; 135—145°/25 mm., 0·95 g., $n_D^{20°}$ 1·4482; 145—151°/25 mm., 10·5 g., $n_D^{20°}$ 1·4494. Two further distillations of the last fraction separated some lower-boiling material and gave a main fraction, b. p. 144—146°/22 mm., $n_D^{20°}$ 1·4509. This on further distillation appeared to be homogeneous as judged by the refractive indexes of each successive fraction. The *substance* was a clear viscous liquid which is stable to N/100-permanganate for at least ½ hour [Found (specimens from two different preparations): C, 70·5, 75·0; H, 11·85, 12·0. $C_{14}H_{32}O_2$ requires C, 70·5; H, 11·9%].

On being heated with 2 : 4-dinitrophenylhydrazine in aqueous-alcoholic sulphuric acid (50%), it yielded a paste of crystals from which a red substance was obtained, needles from glacial acetic acid or ethyl acetate, m. p. 204°. This was identical in every respect with the pyrazoline obtained by a similar method from 1 : 2-epoxy-2 : 4 : 4-trimethylpentan-3-ol.

Reaction with *p*-nitrobenzoyl chloride in pyridine gave a semi-solid product which was separated by means of alcohol into a viscid syrup (*A*) and a crystalline product (*B*). Fractional crystallisation of (*B*), first from alcohol and then from light petroleum, gave a pure *mono*-p-*nitrobenzoate*, slender needles from light petroleum, m. p. 126° (Found: C, 65·4, 65·5; H, 8·3, 8·1; N, 2·9. $C_{23}H_{35}O_6N$ requires C, 65·5; H, 8·4; N, 3·3%). No complete separation of a second substance was achieved. An analysis of the crystalline material, m. p. 96—98°, from the most soluble fraction gave the same results as for the pure ester (Found: C, 65·4; H, 8·2%).

The viscid syrup (*A*) was partially resolved by chromatographic adsorption on alumina into more crystalline material. The less strongly adsorbed material was hydrolysed with aqueous-alcoholic alkali to yield *p*-nitrobenzoic acid and an oil, b. p. 141—143°/19 mm., $n_D^{20°}$ 1·4501, having a composition approximating to that of the original material (Found: C, 71·1; H, 11·5. $C_{14}H_{32}O_2$ requires C, 70·5; H, 11·9%). By reaction with 2 : 4-dinitrophenylhydrazine it gave a pyrazoline identical with the original material.

The following table summarises the yields obtained in some of these preparations.

Reactants (g.).			Products (g.).		
Peracetic acid.	β-Di*iso*-butylene.	Other substances.	Crude unsat. alc., b. p. 145—160°.	Glycol, m. p. 65—66°.	B. p. 130—150°/25 mm.
46	80	Sulphuric acid (3 g.)	15·1	14·9	10·5
65	96	Sulphuric acid (4 g.)	26	24	19
91	126	Sulphuric acid (4·5 g.)	30·4	?	5·4
75	120	Sodium acetate (10 g.)	23	35·5	12

Reaction with Performic Acid.—The method for the preparation of performic acid described by Swern, Billen, Findley, and Scanlan (*J. Amer. Chem Soc.*, 1945, **67**, 1786) was used.

Concentrated hydrogen peroxide (140 c.c., 30%) was added slowly and regularly to an efficiently stirred solution of freshly distilled β-di*iso*butylene (120 g.) in 500 g. of anhydrous formic acid (commerial, 98—100%). The reaction is exothermic, and the temperature was kept below 35° by an external bath of running water. The addition required 2 hours and the reaction was completed by keeping the mixture for 18 hours at room temperature.

The product was isolated by neutralising the formic acid with 50% aqueous sodium hydroxide. The oil which separated was removed with the aid of ether and then heated with aqueous-alcoholic sodium hydroxide to hydrolyse any formic esters that might have been formed.

The hydrolysis solution was diluted with water and extracted several times with ether. The dried extracts, after removal of solvent, left a viscous syrup which solidified on cooling. Trituration with cold light petroleum (b. p. 40—60°) left pure 2 : 4 : 4-trimethylpentane-2 : 3-diol as a white crystalline mass, m. p. 65—66.°

The light petroleum extracts were separated by distillation into three main fractions: (*a*) b. p. 110—175°, (*b*) 2 : 4 : 4-trimethylpentane-2 : 3-diol, b. p. 100—110°/25 mm., (*c*) b. p. 110—150°/20 mm.

Examination of fraction (a).

A preliminary distillation gave the following fractions: 110—130°, 0·60 g., $n_D^{20°}$ 1·4148; 130—143°, 0·85 g., $n_D^{20°}$ 1·4180 (solid separated); 143—153°, 3·65 g., $n_D^{20°}$ 1·4221 (solid separated); 153—163°, 2·60 g., $n_D^{20°}$ 1·4249; 163—173°, 0·75 g., $n_D^{20°}$ 1·4259; 173—175°, 0·90 g., $n_D^{20°}$ 1·4256. The residue on fractionation under reduced pressure gave some glycol.

The refractive index of the lower-boiling fractions suggests the presence of epoxide. They were mixed with aqueous alcohol and kept for 3 weeks at room temperature. On redistillation the fractions up to 145° partly solidified. The higher-boiling fractions, b. p. 145—165°, had $n_D^{20°}$ 1·4242—1·4251, and were unsaturated and alcoholic. From these a 3 : 5-dinitrobenzoate, m. p. 123°, was obtained, identical with that of 2 : 4 : 4-trimethylpent-1-en-3-ol. There was also present a second dinitrobenzoate which could not be isolated in a pure state.

Examination of fraction (c).

Fractional distillation gave the following results: <100°/25 mm., 4·5 g. (chiefly glycol); 100—120°/25 mm., 0·95 g.; 120—135°/25 mm., 0·40 g.; 135—143°/25 mm., 3·70 g., n_D 1·4456.

The last fraction, on being heated with 2 : 4-dinitrophenylhydrazine in aqueous alcoholic 50% sulphuric acid, gave a yellow dinitrophenylhydrazone not identified and the red pyrazoline, m. p. 204°, previously obtained from 1 : 2-epoxy-2 : 4 : 4-trimethylpentan-3-ol.

In this preparation a total of 67·6 g. of 2 : 4 : 4-trimethylpentane-1 : 2-diol was obtained with 3·7 g. of high boiling product and 6·25 g. of low-boiling alcohols, chiefly 2 : 4 : 4-trimethylpent-1-en-3-ol.

A second preparation using β-di*iso*butylene (73 g.), hydrogen peroxide (80 c.c., 30%), and formic acid (300 c.c.), gave 39·4 g. of pure glycol, 5·95 g. of low-boiling alcohols, b. p. 143—163°, and 3·0 g. of high-boiling product, b. p. 135—143°/25 mm.

This work was carried out in the Department of Chemical Engineering as part of a programme sponsored and financed by the Institute of Petroleum. The authors acknowledge their indebtness to Professor Garner, O.B.E., who has generously provided accommodation and facilitated the progress of this research in every possible way. Acknowledgment is made of the assistance given by Mr. R. H. Hill in the practical work. The authors also wish to acknowledge the assistance rendered by Dr. C. Porter in providing analyses on key substances.

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72. *A Study of the Properties of Fluorine-substituted 5-Aminoacridines and Related Compounds. Part III. Some 5-Amino-1 : 2 : 2′ : 3′-Pyridoacridines.*

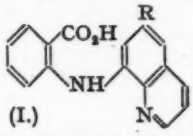
By J. H. Wilkinson and I. L. Finar.

The preparation of *5-amino-1 : 2 : 2′ : 3′-pyridoacridine* and its *4-fluoro-* and *4-methoxy-* derivatives from the corresponding 6-substituted 8-aminoquinolines is described. The three compounds have been examined for antibacterial and trypanocidal activity.

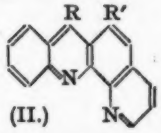
In furtherance of our plan to study fluorine-substituted 5-aminoacridines, we now report the preparation of *4-fluoro-5-amino-1 : 2 : 2′ : 3′-pyridoacridine* (II, R = NH_2, R′ = F) which has

been submitted for antibacterial and trypanocidal tests. *5-Amino-1 : 2 : 2′ : 3′-pyridoacridine* (II, R = NH_2; R′ = H) and its *4-methoxy*-derivative (II, R = NH_2; R′ = OMe) have been prepared for comparison. While this work was in progress, Dobson and Kermack (*J.*, 1946, 150) described the preparation of a number of substituted 5-amino-1 : 2 : 2′ : 3′-pyridoacridines which were examined as potential antimalarials.

The new compounds were prepared by the same route as that used by Dobson and Kermack, namely, by cyclisation of the corresponding *N*-(8′-quinolyl)anthranilic acid, which was obtained by Ullmann condensation of the appropriate 8-aminoquinoline with *o*-halogeno-benzoic acids.



(I.)



(II.)

Since Swarts (*Rec. Trav. chim.*, 1915—1916, **35**, 139) has drawn attention to the poor yield obtained on nitration of *p*-fluoroacetanilide with acetyl nitrate in acetic anhydride, we decided to use ethyl nitrate as nitrating agent in a sulphuric acid medium. A yield of 85% of pure 4-fluoro-2-nitroacetanilide was obtained. Hydrolysis with 8N-hydrochloric acid gave the corresponding nitroaniline which was converted into *6-fluoro-8-nitroquinoline* by the Skraup method, as modified by Richter and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 396). Reduction to *6-fluoro-8-aminoquinoline* was effected by refluxing with reduced iron and alcohol. The product was condensed with *o*-chlorobenzoic acid to give *N-(6′-fluoro-8′-quinolyl)anthranilic acid* (I, R = F). In view of the low yield of *N*-(6′-chloro-8′-quinolyl)anthranilic acid (I; R = Cl) obtained when 6-chloro-8-aminoquinoline was used, we did not consider it worth while proceeding with the preparation of 4-chloro-5-amino-1 : 2 : 2′ : 3′-pyridoacridine at present, unless the biological results on other compounds of this type indicated high activity. *N*-(8′-Quinolyl)-anthranilic acid (I, R = H) and its 6′-methoxy-derivative (I, R = OMe) were prepared by Dobson and Kermack (*loc. cit.*) in 66% and 64% yields respectively, and our results in these preparations substantially confirmed their yields.

Ring closure with phosphorus oxychloride gave *5-chloro-4-fluoro-1 : 2 : 2′ : 3′-pyridoacridine* (II, R = Cl, R′ = F) and its analogues, and these were converted into the corresponding 5-amino-compounds by treatment with ammonium carbonate in phenol. The monohydrochlorides of the 5-amino-derivatives were also obtained by treatment of the appropriate 5-methoxy-compounds with ammonium chloride (Barber, Wilkinson, and Edwards, *J. Soc. Chem. Ind.*, 1947, **66**, 411).

The bases were orange-yellow substances which resembled 5-aminoacridine in their general properties. 4-Fluoro-5-amino-1 : 2 : 2′ : 3′-pyridoacridine (II, R = NH_2, R′ = F) proved to be markedly less soluble in organic solvents than the 4-methoxy- and non-halogenated derivatives. Its mono- and di-hydrochlorides were similarly less soluble in water. In contrast with most 5-aminoacridine hydrochlorides, the hydrochlorides of all three bases exhibited little or no fluorescence in dilute solution by daylight. All three bases readily gave diacetyl derivatives when refluxed with acetic anhydride. These crystallised well and closely resembled 5-diacetylaminoacridine (Wilkinson and Finar, *J.*, 1946, 115).

5-Amino-1 : 2 : 2′ : 3′-pyridoacridine and its 4-fluoro- and 4-methoxy-derivatives showed no trypanocidal activity against *T. equiperdum*, and, although bactericidally active, were not sufficiently so to render them of any practical importance.

Experimental.

(M. ps. are corrected.)

4-Fluoro-2-nitroaniline.—*p*-Fluoroacetanilide (25 g.) was dissolved in sulphuric acid (75 c.c.) and the solution cooled to 0°. Ethyl nitrate (13·75 c.c., 5% excess) was added over a period of 45 minutes at 0—2° with mechanical stirring, after which the mixture was kept at 0° for a further 15 minutes. 4-Fluoro-2-nitroacetanilide (27·3 g., 85%) was isolated by pouring the mixture on crushed ice (400 g.); m. p. 71° (Swarts, *loc. cit.*, gives m. p. 71·5°). The anilide (10 g.) was hydrolysed by refluxing it with 8N-hydrochloric acid (25 c.c.) for 15 minutes, cooling, and making the mixture alkaline with sodium hydroxide (10 c.c., 50%). The product separated as a red oil which hardened on standing to an orange-red solid (7·69 g., 96%); m. p. 93—94° (Swarts, *loc. cit.*, gives m. p. 92·5°).

6-Fluoro-8-nitroquinoline.—4-Fluoro-2-nitroaniline (3 g.) was dissolved in anhydrous glycerol (7·2 g.); arsenic pentoxide (3·3 g.) was added and the mixture treated with sulphuric acid (4 g.) at such a rate that the temperature did not exceed 130°. The mixture was heated at 130—135° for 4 hours, then at 160° for 30 minutes. The cooled solution was treated with water (50 c.c.) and then with ammonia to precipitate the product which was collected and dried. Extraction (Soxhlet) with benzene gave pure

6-*fluoro*-8-*nitroquinoline* (2·31 g., 61·5%) as buff-coloured silky needles, m. p. 121° (Found: C, 56·5; H, 2·8; N, 14·6. $C_9H_5O_2N_2F$ requires C, 56·4; H, 2·6; N, 14·6%).

6-*Fluoro*-8-*aminoquinoline*.—A solution of the fluoronitroquinoline (3 g.) in 70% alcohol (50 c.c.) was refluxed with reduced iron (9 g.) and calcium chloride (0·6 g.) for 5 hours. The mixture was filtered and the bulk of the alcohol was removed from the filtrate. The residue was diluted with water, and the product extracted with ether and distilled. 6-*Fluoro*-8-*aminoquinoline* was obtained as a pale yellow oil (2·03 g., 79%), b. p. 110°/0·15 mm., which solidified on standing to a colourless waxy solid, m. p. 49° (Found: N, 17·2. $C_9H_7N_2F$ requires N, 17·3%).

N-(6′-*Fluoro*-8′-*quinolyl*)*anthranilic Acid*.—*o*-Chlorobenzoic acid (2·22 g.) was dissolved in amyl alcohol (10 c.c.) and the solution treated with anhydrous potassium carbonate (4 g.). 6-Fluoro-8-aminoquinoline (2·3 g.) and copper-bronze catalyst (0·1 g.) were added; the mixture was refluxed for 5 hours, after which the solvent was removed by steam distillation. The residue was filtered and the filtrate acidified with 2N-acetic acid. The product was dissolved in hot 4N-hydrochloric acid, and the solution filtered (charcoal). The purified product (1·5 g., 36%) was isolated by precipitation with aqueous sodium acetate solution. N-(6′-*Fluoro*-8′-*quinolyl*)*anthranilic acid* crystallised from benzene in pale yellow needles, m. p. 234° (decomp.) (Found: C, 67·9; H, 4·05; N, 9·7. $C_{16}H_{11}O_2N_2F$ requires C, 68·1; H, 3·9; N, 9·9%).

5-*Chloro*-4-*fluoro*-1 : 2 : 2′ : 3′-*pyridoacridine*.—*N*-(6′-Fluoro-8′-quinolyl)anthranilic acid (1·4 g.) was refluxed with phosphorus oxychloride (5 c.c.) for 30 minutes, after which the excess of oxychloride was removed by distillation. The residue was dissolved in chloroform (30 c.c.) and poured into ammonia (*d* 0·88, 50 c.c.) cooled with ice. The chloroform layer was separated and the solvent removed, finally under reduced pressure. The residue (1·22 g., 87%) afforded pure 5-*chloro*-4-*fluoro*-1 : 2 : 2′ : 3′-*pyridoacridine* on crystallisation from benzene. It was obtained in small pale yellow prisms, readily soluble in alcohol; m. p. 207—208° (Found: N, 9·7. $C_{16}H_8N_2ClF$ requires N, 9·9%).

4-*Fluoro*-5-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine*.—5-Chloro-4-fluoro-1 : 2 : 2′ : 3′-pyridoacridine (1·7 g.) was refluxed with a solution of sodium methoxide prepared from sodium (0·15 g.) and methanol (20 c.c.) for 30 minutes. Benzene (50 c.c.) was added to the cooled solution which was then treated with water (100 c.c.). The benzene layer was separated and dried (K_2CO_3). The solvent was removed by distillation, and the residue (1·4 g., 84%) crystallised from benzene. 4-*Fluoro*-5-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* was obtained in pale yellow needles, m. p. 184°, readily soluble in alcohol, benzene, and aqueous acetic acid (Found: N, 9·8. $C_{17}H_{11}ON_2F$ requires N, 10·1%).

4-*Fluoro*-5-*amino*-1 : 2 : 2′ : 3′-*pyridoacridine*.—4-Fluoro-5-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) and ammonium chloride (0·12 g.) were dissolved in 85% methanol (5 c.c.). The solution was maintained at 60° for 6 hours, after which the solvent was removed. The residue was dissolved in hot water and filtered from a little unreacted methoxy-compound. The filtrate was made alkaline with 2N-sodium hydroxide. The product was collected, washed free from alkali, and dried at 100° (0·41 g., 87%). 4-*Fluoro*-5-*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* crystallised from pyridine in short yellow hexagonal prisms, m. p. 297—298°. It was sparingly soluble in alcohol, benzene, and xylene (Found: C, 72·8; H, 3·9; N, 15·9. $C_{16}H_{10}N_2F$ requires C, 73·0; H, 3·85; N, 15·97%). The same product was also obtained by heating a mixture of 5-chloro-4-fluoro-1 : 2 : 2′ : 3′-pyridoacridine (1·25 g.), phenol (3 g.), and ammonium carbonate (0·31 g., 20% excess) at 120° for 1 hour. Acetone (25 c.c.) was added to precipitate the hydrochloride of the 5-amino-compound which was converted into the base (36 g., 74%) as described above. The monohydrochloride was obtained as a pale yellow powder, soluble in water and alcohol to give solutions which exhibited a faint blue fluorescence on dilution. When the base (0·1 g.) was refluxed with acetic anhydride (0·5 c.c.) for 5 minutes and the mixture treated with water (5 c.c.), the *diacetyl* derivative (0·11 g.) was obtained. This crystallised from 60% alcohol in pale yellow rhombic plates, m. p. 227—228° (decomp., charring *ca.* 220°). It was soluble in alcohol, but sparingly soluble in benzene. In ultra-violet light an alcoholic solution exhibited a blue fluorescence which became more intense on the addition of alkali (Found: N, 12·05. $C_{20}H_{14}O_2N_2F$ requires N, 12·1%).

N-(8′-*Quinolyl*)*anthranilic Acid*.—*o*-Iodobenzoic acid (6·2 g.) was dissolved in amyl alcohol (25 c.c.) and treated with anhydrous potassium carbonate (3·5 g.). 8-Aminoquinoline (3·6 g.) and copper bronze catalyst (0·5 g.) were added and the mixture was refluxed for 4 hours, after which the amyl alcohol was removed by steam distillation. The residue was extracted with boiling water (250 c.c.) and ammonium chloride (50 g.) was added to the filtered extract to precipitate the ammonium salt of the product. The latter was dissolved in dilute alkali and the free acid (4·86 g., 74%) isolated by precipitation with acetic acid. Crystallisation from 70% alcohol gave golden-yellow hexagonal plates, m. p. 247° (Dobson and Kermack, *loc. cit.*, give m. p. 243—244°) (Found: C, 72·8; H, 4·65; N, 10·4. Calc. for $C_{16}H_{12}O_2N_2$: C, 72·7; H, 4·55; N, 10·6%).

5-*Chloro*-1 : 2 : 2′ : 3′-*pyridoacridine*.—*N*-(8′-Quinolyl)anthranilic acid (3 g.) and phosphorus oxychloride (15 c.c.) were refluxed for 1 hour. The excess of oxychloride was removed under reduced pressure, and the residue dissolved in chloroform (100 c.c.). The product was isolated as described for the 4-fluoro-derivative and crystallised from 70% alcoholic ammonia (N/30). 5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine monohydrate (2·2 g., 73%) was obtained in pale yellow, almost colourless, needles, m. p. 164° (Dobson and Kermack, *loc. cit.*, give m. p. 165°) (Found: N, 9·8. Calc. for $C_{16}H_9N_2Cl,H_2O$: N, 9·9%). The *anhydrous* form was obtained by drying at 100°. The m. p. (164°) was unchanged on subsequent crystallisation from dry benzene (Found: N, 10·7. $C_{16}H_9N_2Cl$ requires N, 10·6%).

5-*Methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine*.—5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine (2·92 g.) was refluxed for 30 minutes with sodium methoxide (0·65 g., 10% excess) in methanol (30 c.c.). The 5-methoxy-derivative separated as an oil on the addition of water (100 c.c.) to the cooled solution. It was extracted with benzene, and the extract was concentrated to about 10 c.c. An equal volume of light petroleum (b. p. 80—100°) was added. 5-*Methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* crystallised in buff-coloured needles (2·28 g., 79%), m. p. 167—168°, readily soluble in benzene and alcohol but sparingly soluble in ether (Found: N, 10·9. $C_{17}H_{12}ON_2$ requires N, 10·75%).

5-*Amino*-1 : 2 : 2′ : 3′-*pyridoacridine*.—5-Methoxy-1 : 2 : 2′ : 3′-pyridoacridine (2·2 g.) and ammonium

chloride (0·55 g., 20% excess) were dissolved in 90% alcohol (30 c.c.) and the solution maintained at 60° for 14 hours. The mixture was evaporated to about 10 c.c. and the hydrochloride of the product collected by filtration. After being washed with acetone and dried at 100°, it was dissolved in boiling water (70 c.c.) and filtered from the small amount of 1 : 2 : 2′ : 3′-pyridoacridone, m. p. 275°. The filtrate was treated with alkali to precipitate the product (2·2 g., 82%). *5-Amino*-1 : 2 : 2′ : 3′-*pyridoacridine* crystallised from 70% alcohol in orange-yellow triangular prisms, m. p. 252° with preliminary softening (Found : C, 76·2; H, 5·2; N, 15·55. $C_{16}H_{11}N_3,\frac{1}{2}C_2H_5OH$ requires C, 76·1; H, 5·2; N, 15·7%) When dried at 130°/12 mm., the alcohol of crystallisation was removed (loss : 8·2; calc. : 8·6%), and the *base* was obtained in orange prisms, highly soluble in most organic solvents (Found : C, 78·5; H, 4·6; N, 16·9. $C_{16}H_{11}N_3$ requires C, 78·4; H, 4·5; N, 17·1%). The hydrochloride was a light yellow powder, readily soluble in water and alcohol; the solutions showed a faint blue fluorescence on dilution. The *diacetyl* derivative crystallised from benzene in colourless prisms, m. p. 191—192°. It was highly soluble in alcohol giving a solution which exhibited a violet fluorescence in ultra-violet light (Found : N, 12·5. $C_{20}H_{15}O_2N_3$ requires N, 12·75%).

N-(6′-Methoxy-8′-quinolyl)anthranilic acid (16·5 g., 56%) was prepared from *o*-iodobenzoic acid (24·9 g.), 6-methoxy-8-aminoquinoline (19·1 g., 10% excess), potassium carbonate (14 g.), copper-bronze catalyst (0·5 g.), and water (100 c.c.), substantially as described for *N*-(8′-quinolyl)anthranilic acid. The product crystallised from alcohol in pale yellow prisms, m. p. 207° (Dobson and Kermack, *loc. cit.*, report m. p. 201°) (Found : N, 9·5. Calc. for $C_{17}H_{14}O_3N_2$: N, 9·5%).

5-Chloro-4-methoxy-1 : 2 : 2′ : 3′-*pyridoacridine*.—*N*-(6′-Methoxy-8′-quinolyl)anthranilic acid (10 g.) was refluxed with phosphorus oxychloride (20 c.c.) for 2 hours, after which the phosphorus oxychloride was removed by distillation. The product (10 g., quantitative) was isolated as described for 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine. It crystallised from 90% alcoholic ammonia (N/30) in golden yellow needles, m. p. 105—106°, which appeared to be hydrated since when heated at 78°/18 mm. water was lost and the m. p. rose to *ca.* 170° (Dobson and Kermack, *loc. cit.*, give m. p. 169°) (Found : N, 9·3. Calc. for $C_{17}H_{11}ON_3Cl$: N, 9·5%).

4 : 5-*Dimethoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* was prepared by refluxing 5-chloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (3·12 g.) with a solution of sodium methoxide prepared from sodium (0·3 g.) and anhydrous methanol (20 c.c.) for 30 minutes. It was isolated as described for the other 5-methoxy-derivatives; it crystallised from 50% methanol in pale buff-coloured rhombs, m. p. 205° (Found : N, 9·75. $C_{18}H_{14}O_3N_2$ requires N, 9·65%).

5-Amino-4-methoxy-1 : 2 : 2′ : 3′-*pyridoacridine*.—A solution of 4 : 5-dimethoxy-1 : 2 : 2′ : 3′-pyridoacridine (3·6 g.) and ammonium chloride (0·83 g., 20% excess) in 90% alcohol (25 c.c.) was heated at 60° for 8 hours, after which the alcohol was evaporated and the hydrochloride of the product (3·14 g., 81%) collected by filtration. This was dissolved in water (30 c.c.) and treated with sodium hydroxide to precipitate the *base* (2·43 g.), which crystallised from 40% alcohol in yellowish-brown prisms, highly soluble in most organic solvents, m. p. 220° (Found : C, 68·6; H, 5·2; N, 14·4. $C_{17}H_{13}ON_3,H_2O$ requires C, 69·6; H, 5·2; N, 14·35%). The dihydrochloride crystallised from water in orange-yellow prisms, soluble in about 2 parts of water, highly soluble in alcohol. A dilute solution was not fluorescent by daylight but exhibited a faint green fluorescence in ultra-violet light. When dried at 130°/10 mm., water and hydrogen chloride were lost and the residue consisted of the *monohydrochloride*. This was obtained in orange prisms, m. p. *ca.* 360° (Found : N, 13·25; Cl, 11·5. $C_{17}H_{13}ON_3,HCl$ requires N, 13·5; Cl, 11·4%). The *diacetyl* derivative crystallised from alcohol in pale yellow highly refractive plates, sparingly soluble in alcohol, m. p. 255—256° (decomp.) (Found : N, 11·3. $C_{21}H_{17}O_3N_3$ requires N, 11·7%).

N-(6′-Chloro-8′-quinolyl)anthranilic acid was prepared by refluxing a mixture of 6-chloro-8-aminoquinoline (4·46 g.), *o*-chlorobenzoic acid (3·91 g.), potassium carbonate (3·5 g.), and copper–bronze catalyst (0·1 g.) in amyl alcohol (15 c.c.) for 8 hours, after which the solvent was removed by steam distillation. The residue was extracted with hot water and the product (0·82 g.) isolated by acidification of the filtered extract with acetic acid. It was a pale yellow powder, sparingly soluble in most organic solvents, but readily soluble in mineral acids and alkalis, m. p. 206—209°. Since crystallisation proved impracticable, the *methyl* ester was prepared by refluxing the acid (0·8 g.) with methanol (4 c.c.) and sulphuric acid (2 c.c.) for 2 hours. The mixture was poured into water (20 c.c.) and the sparingly soluble sulphate of the ester was precipitated. Trituration with ammonia gave the free ester (0·75 g.) which was washed free from non-esterified acid with ammonia solution followed by water. It crystallised from methanol in bright yellow needles, m. p. 132° (Found : C, 65·3; H, 4·3; N, 8·9. $C_{17}H_{13}O_2N_2Cl$ requires C, 65·3; H, 4·15; N, 8·9%).

The authors wish to express their thanks to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-micro analyses, to the Biological Division, May and Baker Ltd., for the biological results, and to Dr. H. J. Barber and the directors of May and Baker Ltd. for facilities kindly placed at the disposal of one of them (J. H. W.).

S.W. Essex Technical College, Forest Road, E. 17.
Research Laboratories, May and Baker Ltd., Dagenham, Essex.

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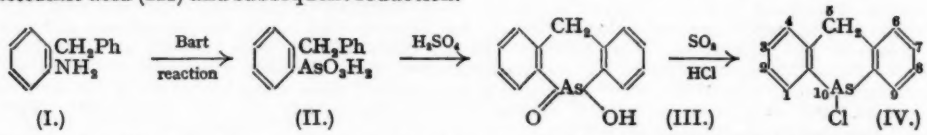
73. *Derivatives of Arsacridine. Part I.*

By C. L. Hewett, L. J. Lermit, H. T. Openshaw, A. R. Todd, A. H. Williams, and F. N. Woodward.

2-Aminodiphenylmethane has been prepared from phthalic anhydride in 53% yield by a four-stage process. Its conversion into 10-chloro-5 : 10-dihydroarsacridine (IV) (Gump and Stoltzenberg, *J. Amer. Chem. Soc.*, 1931, **53**, 1428) has been improved. The 2-*methyl* derivative of (IV) has been prepared in a similar manner, and (IV) has been converted into 10-*cyano*-5 : 10-*dihydroarsacridine*.

A re-examination of the physiological properties of a number of arsenical heterocyclic compounds (carried out during the war at the Chemical Defence Research Establishment, Porton) showed that 10-chloro-5 : 10-dihydroarsacridine * (IV) possessed outstanding sternutatory activity. This substance had been prepared by Gump and Stoltzenberg (*loc. cit.*) by conversion of 2-aminodiphenylmethane (I) into the arsonic acid (II), followed by cyclisation to arsacridinic acid (III) and subsequent reduction.



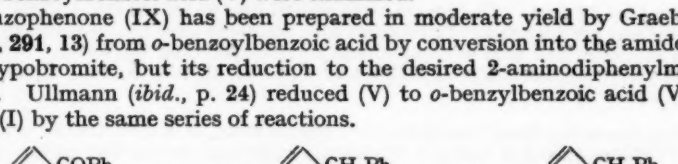
(I.) (II.) (III.) (IV.)

The amine (I) was prepared from *o*-nitrobenzyl chloride by a Friedel–Crafts reaction with benzene and subsequent reduction. The scarcity of toluene, together with the low conversion efficiencies from toluene to *o*-nitrobenzyl chloride, and *o*-nitrobenzyl chloride to the amine (I), made this method of synthesis quite unsuitable for bulk production, and alternative routes were therefore sought.

No appreciable reaction occurred when diphenylmethane was heated with arsenic trichloride alone or in the presence of mercuric chloride or stannic chloride. When aluminium chloride was used as catalyst, a vigorous reaction ensued with decomposition of some of the diphenylmethane (Scholl and Seer, *Ber.*, 1922, **55**, 338), but none of the desired product (IV) could be isolated from the reaction mixture. Attempts were made to condense diphenylchloroarsine with methylene chloride, in the presence of aluminium chloride, in a variety of solvents (carbon disulphide, tetrachloroethane, and nitrobenzene) and at various temperatures, with negative results. Freshly prepared aluminium bromide being used with carbon disulphide as solvent, a vigorous reaction set in, but the only product was a black tar, together with unchanged diphenylchloroarsine. Similarly, attempted condensation of paraformaldehyde with diphenylchloroarsine in the presence of phosphoric oxide, sulphuric acid, or phosphorus oxychloride at 200—250° afforded only unworkable black tars.

In view of the lack of success of these direct condensation methods further investigation was limited to improvement of the method of Gump and Stoltzenberg, and in particular to finding a satisfactory method for the preparation of 2-aminodiphenylmethane. Two alternative routes starting from *o*-benzoylbenzoic acid (V) were examined.

2-Aminobenzophenone (IX) has been prepared in moderate yield by Graebe and Ullmann (*Annalen*, 1896, **291**, 13) from *o*-benzoylbenzoic acid by conversion into the amide and treatment with sodium hypobromite, but its reduction to the desired 2-aminodiphenylmethane has not been described. Ullmann (*ibid.*, p. 24) reduced (V) to *o*-benzylbenzoic acid (VI) but failed to convert it into (I) by the same series of reactions.



(V.) (VI.) (VII.) (VIII.) (IX.) (I.)

In view of the ready accessibility of *o*-benzoylbenzoic acid and the good yield (80%) of the reduced acid (VI) obtained by zinc dust and ammonia reduction (Barnett, Cook, and Nixon,

* The numbering of the arsacridine ring follows the acridine numbering customary in the *Journal*.—Editor.

J., 1927, 504) the possibilities of the latter route were first investigated. However, the findings of Ullmann were confirmed, the amide (VII) on treatment with sodium hypobromite giving only a small amount of an amine which was not 2-aminodiphenylmethane. It is probable that the main reaction is substitution of the methylene group by bromine, a reaction which cannot occur with *o*-benzoylbenzamide.

Attention was therefore turned to the alternative route involving the reduction of 2-aminobenzophenone (IX). Of the various methods tried only sodium and ethyl or amyl alcohol was effective; amalgamated zinc and hydrochloric acid under various conditions gave a brown resin; zinc dust and glacial acetic acid reduced only as far as 2-aminobenzhydrol; iron filings and acetic acid were without effect. Attempts to effect the reduction electrolytically and catalytically (Raney nickel) were without success, although high-pressure hydrogenation with a copper chromite catalyst afforded 33% conversion. The reduction by the sodium and alcohol method was sufficiently effective, however, to make this route attractive provided that Graebe and Ullmann's conversion of the acid (V) into the amine (IX) could be improved.

Attempts to convert the acid (V) or its methyl ester directly into the amide by the action of ammonia were unsuccessful, but the number of operations required to carry out this conversion by the published method (Graebe and Ullmann, *loc. cit.*) through the acid chloride has been reduced and the yield increased to 80%. The original Hofmann degradation of the amide (VIII) to the amine (IX) was considerably improved by the addition of bromine to the alkaline solution of (VIII) in place of using preformed sodium hypobromite, and even better results were obtained by using sodium hypochlorite. The overall yield of 2-aminodiphenylmethane (I) from phthalic anhydride was thus raised to 53%.

The Bart reaction for the conversion of (I) into the arsonic acid (II) was re-investigated; by using a " simultaneous addition " technique under conditions of controlled pH (Booker, Murray, Spring, Stanley, and Todd, forthcoming publications) the yield was raised to 50%. Even better results were obtained by using a modification of the Doak procedure. Under the original conditions of the Doak method (*J. Amer. Chem. Soc.*, 1940, **62**, 167) 2-aminodiphenylmethane gave poor and variable yields of arsonic acid; among other products a considerable amount of fluorene was always obtained. Consistent yields of 70—75% were obtained, however, when the method was modified by increasing the amount of arsenic trichloride to 100% excess, lowering the temperature of diazotisation and increasing the quantity of cuprous bromide from a catalytic amount to slightly more than one molar equivalent.

The final stages of the synthesis, involving the cyclisation of (II) to arsacridinic acid (III), followed by reduction to (IV), presented no difficulty and gave an 85% yield of crude product. By an analogous series of reactions, 2-*p*-toluoylbenzoic acid was converted into 2-amino-4'-methylbenzophenone (Kippenberg, *Ber.*, 1897, **30**, 1133), which was reduced to 2-*amino*-4'-*methyldiphenylmethane*, from which 10-*chloro*-2-*methyl*-5 : 10-*dihydroarsacridine* was obtained. Interaction of (IV) with potassium cyanide yielded 10-*cyano*-5 : 10-*dihydroarsacridine* which proved to be an even more powerful sensory irritant than the chloro-compound.

Experimental.

o-*Benzoylbenzamide*.—*o*-Benzoylbenzoic acid monohydrate (108 g.) was dehydrated by heating in a basin on the water-bath for 1½ hours, with frequent stirring and crushing. The dehydrated acid (100 g.) was dissolved in dry chloroform (200 c.c.) and after the addition of thionyl chloride (40 c.c.) was warmed gently under reflux on the water-bath until reaction was complete. The solvent and excess of thionyl chloride were distilled off, the last traces being removed by distillation with dry benzene (20 c.c.) in a vacuum, this treatment being repeated once.

Without further purification the acid chloride was dissolved in dry benzene (200 c.c.) and slowly treated with ammonia solution (*d* 0·880; 100 c.c.) with cooling. Considerable heat was developed and the whole set to a pasty mass. The crude amide was filtered off and washed with water. It was subsequently found that the purity of the amide greatly influenced the yield in the next stage, specimens of amide with an m. p. below 161—162° giving consistently poor yields of amine. The chief trouble appeared to be due to the retention of ammonium chloride and probably ammonium benzoylbenzoate by the crude amide. Purification could be carried out by recrystallising the crude product (m. p. 150—153°) from dilute alcohol (which raised the m. p. to 155—160°) and then from a large volume of toluene which gave a product of m. p. 161°.

To overcome this troublesome crystallisation another method of purification was sought and it was found that the crude amide (from 100 g. of dehydrated acid) was readily purified by washing twice more, preferably by grinding in a mortar, with hot water. By this treatment the m. p. was raised directly to 160—161°, one crystallisation from 40% alcohol raising it to 162—163° (yield, 75—80 g.; 75—80%).

2-*Aminobenzophenone*.—(a) Pure *o*-benzoylbenzamide (45 g.; m. p. 161°) was added to a solution of sodium hydroxide (20 g.; 2½ mols.) in water (150 c.c.); the amide dissolved completely and rapidly. The solution was cooled in ice and a slight excess (*ca.* 5%) of sodium hypochlorite solution (97 c.c. of a solution containing 0·075 g. of chlorine per c.c. as sodium hypochlorite) added slowly with shaking or

stirring; little heat was developed. The clear solution was warmed on a water-bath to about 80°, whereupon the amine began to separate as fine yellow droplets. The mixture was heated for a further ½ hour at 100° and cooled, and the amine which readily crystallised was collected; yield 33—36 g. (85—92%), m. p. 95—102°. Recrystallised from alcohol, it had m. p. 107° (Geigy and Kŏnigs, *Ber.*, 1885, **18**, 2403, give m. p. 105—106°; Carré, *Compt. rend.*, 1909, **148**, 493, gives 110—111°).

(b) The pure amide (45 g.; m. p. 161°) was dissolved in sodium hydroxide solution (300 c.c.; 15%) and cooled to 0° in ice; bromine (10·2 c.c.) was then added dropwise with stirring. The mixture was then heated as under (a), and the amine collected on cooling; this was usually slightly less pure (m. p. 90—100°) than that obtained as described under (a); yield 80—85%.

Reduction of 2-Aminobenzophenone.—(a) *Reduction with sodium and alcohol.* The pure amino-ketone (10 g.) was dissolved in absolute alcohol (100 c.c.), and the hot solution rapidly added to small pieces of sodium (10 g.; 100% excess) in a flask fitted with an efficient reflux condenser. The reaction was allowed to proceed unchecked; when it moderated a further amount of hot alcohol (20 c.c.) was added, and the last of the sodium dissolved by external heating and shaking. The reaction mixture was then diluted with water (250 c.c.), the alcohol removed in a vacuum, and the amine distilled with steam. Distillation was slow, but the product was reasonably pure, and the amine, which came over as a colourless oil, crystallised on cooling. Ether extraction of the aqueous part of the distillate yielded a further amount of amine; total yield, 8·4 g. (90%), m. p. 44°. The pure amine, crystallised from light petroleum, had m. p. 52° (Carré, *Compt. rend.*, 1909, **148**, 102, gives m. p. 52°). The acetyl derivative crystallised from dilute alcohol; m. p. 130° (Fischer and Schutte, *Ber.*, 1893, **26**, 3086, give m. p. 135°). The benzoyl derivative, from dilute alcohol, had m. p. 116° (Fischer and Schmidt, *Ber.*, 1894, **27**, 2786, give m. p. 116°).

(b) *Reduction with sodium and amyl alcohol.* The amino-ketone (10 g.) was dissolved in hot *iso*amyl alcohol (b. p. 129—131°; 100 c.c.), and the boiling solution added all at once to small pieces of sodium (10 g.). The reaction was much slower than when using ethyl alcohol; towards the end of the reaction a further 20 c.c. of amyl alcohol were added, and the last traces of sodium dissolved by heating and shaking. Water (200 c.c.) was then added and after thorough shaking the aqueous layer was removed and the amyl alcohol distilled with steam. The residual crude amine was dissolved in benzene (40 c.c.), and the solution shaken with concentrated hydrochloric acid until the hydrochloride crystallised; this was filtered off, washed with benzene, and dried. On treatment with dilute ammonia it gave the amine as a colourless solid, m. p. 49—50° (yield, 80%). An alternative method of isolation involving distillation of the crude amine with superheated steam followed by distillation at reduced pressure gave a higher yield (92%), but the product was not as pure and did not crystallise readily.

When the quantity of sodium was reduced to 60% instead of 100% excess, the experiment remaining the same in all other respects, the same quantity and quality of amine were obtained.

(c) *High-pressure hydrogenation of 2-aminobenzophenone.* The amino-ketone (200 g.) was hydrogenated at high pressure and at a temperature of 250°, a copper chromite catalyst being employed. About 20 l. (theory, 44 l.) of hydrogen were absorbed in 6 hours and the catalyst was converted into the completely inactive form. The product was taken up in ethanol, filtered from the catalyst, and the ethanol removed by distillation under reduced pressure. The crude product (178 g.) was distilled under reduced pressure and a pale yellow oil (134 g.) was collected at 130—160°/0·2 mm. It consisted of a mixture of *o*-aminodiphenylmethane and *o*-aminobenzophenone, which could not be separated satisfactorily by distillation. By fractional crystallisation of the bases and their hydrochlorides, 2-aminodiphenylmethane hydrochloride (72 g.; 33%) was isolated in a pure condition.

Diphenylmethane-2-arsonic Acid.—(a) *Bart method.* A series of experiments was made in order to determine the relation between the pH of the reaction mixture and yield of product in the coupling of diazotised 2-aminodiphenylmethane and sodium arsenite. It was found that the optimum pH was *ca.* 9·5, but even under the best conditions the yield of arsonic acid could not be increased above 50%, probably because of the instability of the diazo-compound and its tendency to pass into fluorene. The following details refer to the method adopted for large scale preparations:

2-Aminodiphenylmethane hydrochloride (22 g.; 0·1 mol.) was suspended in dilute hydrochloric acid (21 c.c. of 36° Tw. + 180 c.c. of water), cooled to − 5° with stirring, and diazotised with a solution of sodium nitrite (6·9 g.) in water (15 c.c.). The resulting solution was diluted to 250 c.c. with ice-water. Arsenious oxide (19·8 g.; 0·2 equiv.) was dissolved in a solution of sodium hydroxide (12 g.; 0·3 mol.) and sodium carbonate (15·9 g.; 0·3 equiv.) in water (180 c.c.), and the solution diluted to 250 c.c. The two solutions were run simultaneously into a mixture of ice (*ca.* 75 g.) and ammoniacal copper sulphate solution (13 c.c. of 10%) with stirring during 1 hour, the temperature of the mixture being kept below 5°. After the addition was complete stirring was continued for a further 20 minutes, the mixture then no longer giving a colour with an alkaline solution of H-acid. "Filtercel" (*ca.* 10 g.) was added, and the mixture filtered. The filtrate was made neutral to litmus by the careful addition of dilute hydrochloric acid with vigorous stirring. After standing overnight the small amount of precipitate was removed by filtration and the filtrate was made acid to Congo-red by the addition of hydrochloric acid. The product rapidly crystallised. It was collected, washed, and dried at 60° (14 g.; 48%), giving colourless crystals, m. p. 155—156° with previous sintering (lit. 161—162°). By salting out the mother-liquors a further 0·35 g. was obtained.

The purity of the product (average 95—99%) was estimated by titration. Electrometric titration showed that a good end-point could be obtained by titrating only the first ionisable hydrogen, the exact end-point being at pH 6·6 and the pH changing from 7·3 to 6·3 by addition of 0·2 c.c. in a titre of 17 c.c. of N-sodium hydroxide.

Titration method. Approximately 0·6 g. of acid was weighed out accurately, dissolved in 25 c.c. of N-sodium hydroxide, and titrated against N/5-hydrochloric acid, 5 drops of bromocresol-purple (B.D.H.) being added. The solution became colourless at the end point; addition of a further drop of acid produced a distinct yellow colour.

(b) *Doak method.* 2-Aminodiphenylmethane (18·3 g.) was dissolved in absolute alcohol (250 c.c.),

cooled to − 10°, and to the solution were then added, in order, concentrated sulphuric acid (8 c.c.), arsenic trichloride (17 c.c.), and powdered anhydrous calcium chloride (10 g.). The solution was diazotised at − 10° to − 15° with a solution of sodium nitrite (7·2 g.) in water (9 c.c.). The solution was stirred for ½ hour longer at − 10°, urea (1 g.) added to remove any excess of nitrous acid, and then freshly prepared dry cuprous bromide (15 g.) was added gradually, the reaction temperature being kept below − 10°. After being stirred for one hour at − 10° the reaction mixture was allowed to warm slowly to room temperature. Alcohol was removed by steam distillation, the residue diluted with water and cooled, and the crude arsonic acid filtered off and washed. It was purified by dissolving in warm sodium carbonate solution, filtering through charcoal, and acidifying with hydrochloric acid (yield, 21·8 g.; 74%).

Arsacridinic Acid (III).—Following the procedure of Gump and Stoltzenberg (*loc. cit.*) a 95% yield of crude product was obtained.

10-*Chloro*-5 : 10-*dihydroarsacridine* (IV).—Crude arsacridinic acid (12·5 g.) was reduced according to the directions of Gump and Stoltzenberg. The crude product (11·3 g.; 90%) solidified as soon as it was removed from the steam-bath. It was dissolved in hot benzene (50 c.c.) and treated with a little charcoal. The filtered solution was concentrated to small bulk and allowed to crystallise. The product (8·9 g.; 71%) was pale yellow and had m. p. 110—111° (lit. 114—115°).

2-*Amino*-4′-*methyldiphenylmethane*.—2-Amino-4′-methylbenzophenone (Kippenberg, *loc. cit.*) was reduced with sodium and amyl alcohol as described above, giving 2-*amino*-4′-*methyldiphenylmethane* (yield, 65%), which had m. p. 66° after recrystallisation from alcohol or light petroleum (Found : C, 85·3; H, 7·5. $C_{14}H_{15}N$ requires C, 85·4; H, 7·6%). The acetyl derivative, prepared in the usual manner and crystallised from alcohol, had m. p. 171°.

10-*Chloro*-2-*methyl*-5 : 10-*dihydroarsacridine*.—The above amine was converted into 4′-methyldiphenylmethane-2-arsonic acid in 25% yield by the Bart reaction, conditions similar to those employed for the parent substance being used. The crude arsonic acid (2·95 g.) was dissolved in concentrated sulphuric acid (12 c.c.), and the solution heated at 95° for 5 minutes. On pouring into cold water a gum was precipitated; this was dissolved in 10% aqueous sodium carbonate, heated with charcoal, and filtered. Dilute hydrochloric acid was added to the filtrate with stirring until a slight turbidity appeared; charcoal was added, and the mixture filtered. Acidification of the filtrate gave a precipitate (1·4 g.) which crystallised on standing. It was suspended in concentrated hydrochloric acid (14 c.c.), chloroform (14 c.c.) was added, together with a trace of potassium iodide, and reduction with sulphur dioxide was carried out in the usual manner. The chloroform layer on evaporation yielded a brownish oil (1·4 g.) which did not crystallise. It was distilled at 125—140° (bath temp.)/3×10^{-3} mm.; the resulting pale yellow distillate crystallised on standing and then had m. p. 55—60°. Recrystallisation from light petroleum (b. p. 40—60°) yielded 10-*chloro*-2-*methyl*-5 : 10-*dihydroarsacridine* as pale yellow prisms, m. p. 65·5—66·5° (Found : C, 57·5; H, 4·2. $C_{14}H_{13}ClAs$ requires C, 57·8; H, 4·1%).

10-*Cyano*-5 : 10-*dihydroarsacridine*.—Pure potassium cyanide (0·65 g.) was heated under reflux with anhydrous methanol (10 c.c.) until a clear solution was obtained. 10-Chloro-5 : 10-dihydroarsacridine (2·67 g.) was added, and the mixture refluxed for 20 minutes. The chloro-compound rapidly dissolved and a precipitate of potassium chloride was formed. The hot solution was filtered and allowed to cool, whereupon colourless crystals (1·5 g.; 56%) separated. After recrystallisation from anhydrous methanol the *cyanide* had m. p. 114—115°, giving a cloudy liquid. Mixed with the chloride (m. p. 110—111°) the m. p. was depressed to 103—106° (Found : C, 63·1; H, 3·5; N, 4·9. $C_{14}H_{10}NAs$ requires C, 62·9; H, 3·7; N, 5·2%).

Our thanks are due to the Chief Scientist, Ministry of Supply, for permission to publish these results.

THE UNIVERSITY, MANCHESTER.
CHEMICAL DEFENCE RESEARCH ESTABLISHMENT, SUTTON OAK,
ST. HELEN'S, LANCS.

[*Received, April 21st*, 1947.]

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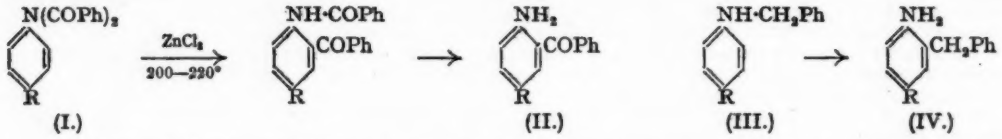
74. *Derivatives of Arsacridine. Part II.*

By R. E. DAVIES, H. T. OPENSHAW, F. S. SPRING, R. H. STANLEY, and A. R. TODD.

4-Substituted 2-aminodiphenylmethanes are readily obtained by the rearrangement of *p*-substituted *N*-benzylanilines under the influence of aluminium chloride in presence of excess of the parent arylamine. Two of these products have been converted into derivatives of arsacridine.

IN the synthesis of derivatives of arsacridine by the method of Gump and Stoltzenberg (*J. Amer. Chem. Soc.*, 1931, **53**, 1428) the principal limitation is the availability of the substituted 2-aminodiphenylmethanes required as intermediates. One method for the preparation of such substances has been described in Part I (preceding paper), but it has the disadvantage of involving a considerable number of stages. In attempting to overcome this difficulty, we first investigated the conversion of diacylanilides of type (I) into the corresponding benzophenone derivatives (II) by the catalytic migration of a benzoyl group (Chattaway, *J.*, 1904, **85**, 589). In the two cases investigated (R = Cl and R = Me), the yields of 5-chloro-2-amino- and 2-amino-5-methyl-benzophenone were 8·8% and 12·3% respectively. The latter compound was

characterised by reduction and acetylation, 2-acetamido-5-methyldiphenylmethane (see below) being obtained.

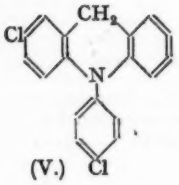


(I.) (II.) (III.) (IV.)

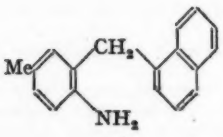
In view of these unsatisfactory yields, attention was turned to the rearrangement of *N*-benzylanilines. Hickinbottom (*J.*, 1937, 1119) obtained a mixture of 2- and 4-aminodiphenylmethanes in moderate yield (31·9%) by heating *N*-benzylaniline with anhydrous cobalt chloride. On applying this procedure to *N*-benzyl-*p*-toluidine (III; R = Me), we obtained a 23·9% yield of 2-amino-5-methyldiphenylmethane (IV; R = Me), characterised as its *acetyl* and p-*nitrobenzylidene* derivatives. The use of aluminium chloride gave a slightly higher yield; zinc chloride was less effective. A considerable quantity of a high-boiling material was also produced in the reaction. It seemed probable that this was, at least in part, composed of 2-benzylamino-5-methyldiphenylmethane or 2 : 6-dibenzyl-*p*-toluidine, formed by attack of a free benzyl radical on a molecule of unchanged *N*-benzyl-*p*-toluidine or of the newly formed 2-amino-5-methyldiphenylmethane (Hickinbottom, *loc. cit.*, observed the formation of 2 : 4-dibenzylaniline in the reaction carried out by him). If this were so, addition of *p*-toluidine to the reaction mixture should increase the yield of the desired product. This proved to be the case; by heating a mixture of equal weights of *N*-benzyl-*p*-toluidine and *p*-toluidine with aluminium chloride, the yield of (IV; R = Me) was raised to 50%. On treating a mixture of *p*-chloroaniline and its *N*-benzyl derivative in the same manner, 5-chloro-2-aminodiphenylmethane (IV; R = Cl), characterised as its *hydrochloride*, was obtained, together with a high-melting product which from its mode of formation and its composition is almost certainly 3-*chloro*-10-p-*chlorophenyl*-5 : 10-*dihydroacridine* (V). 4-*Amino*-m-*tolyl*-α-*naphthylmethane* (VI) was similarly obtained from N-α-*naphthylmethyl*-p-*toluidine* in 68% yield. An attempt to achieve a similar rearrangement of benzoyl-*p*-toluidine, using cobalt chloride as catalyst in presence of excess *p*-toluidine, failed to give any of the desired aminobenzophenone.

The conversion of the aminodiphenylmethanes (IV; R = Me or Cl) into arsacridine derivatives followed the lines described in Part I (preceding paper); 10-*chloro*-3-*methyl* (VII; R = Me; R′ = Cl), 3 : 10-*dichloro*- (VII; R = R′ = Cl) and 3-*chloro*-10-*cyano*-5 : 10-*dihydroarsacridine* (VII; R = Cl, R′ = CN) were thus obtained. Conversion of the amine (VI) into the corresponding arsonic acid appeared to give such low yields that the further stages in the synthesis of a 3 : 4-benzarsacridine derivative from this material were not investigated.

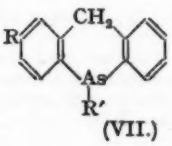
For the preparation of nitro- and amino-derivatives of arsacridine, both the rearrangement of *N*-benzyl-*p*-nitroaniline and the nitration of arsacridinic acid were found impracticable. Nitration of 2-acetamidodiphenylmethane gave, after hydrolysis of the initially formed 5-*nitro*-2-*acetamidodiphenylmethane*, a good yield of 5-*nitro*-2-*aminodiphenylmethane*, but the conversion of this substance into the corresponding acid was not investigated since it was at this stage already clear that the projected synthesis was for various reasons unlikely to be of technical interest.



(V.)



(VI.)



(VII.)

Experimental.

5-*Chloro*-2-*aminobenzophenone*.—A mixture of *p*-chloroaniline (23·8 g.), benzoyl chloride (52·5 g.; 2 mols.), and zinc chloride (1·5 g.) was kept at 220—230° for 14 hours. The mixture was cooled and hydrolysed by refluxing for 60 hours with a mixture of ethyl alcohol (100 c.c.) and concentrated hydrochloric acid (50 g.). Excess of alcohol and ethyl benzoate were removed in a rapid current of steam, the residue decanted from undistillable tarry oil, and made alkaline with sodium hydroxide solution. Superheated steam was then blown through the mixture, *p*-chloroaniline coming over first followed by 5-chloro-2-aminobenzophenone which quickly solidified in yellow flocks; after one crystallisation from chloroform–light petroleum, it had m. p. 97—98° (yield, 3·8 g., 8·8%).

2-*Amino*-5-*methylbenzophenone*.—*p*-Toluidine (22·3 g.), benzoyl chloride (58·6 g.), and zinc chloride

(1·5 g.) were treated as described above, giving 2-amino-5-methylbenzophenone (5·4 g.; 12·3%) which after one crystallisation from chloroform–light petroleum had m. p. 65—66°.

Reduction of 5-Chloro-2-aminobenzophenone.—A solution of 5-chloro-2-aminobenzophenone (2·2 g.) in boiling *iso*amyl alcohol (22 c.c.; b. p. 129—131°) was poured on sodium slices (2·2 g.) heated in an oil-bath to 80°. The reaction was allowed to proceed unchecked but an efficient reflux condenser was employed; when the reaction had moderated, amyl alcohol (5 c.c.) was added and the last traces of sodium were dissolved by heating and shaking. The reaction mixture was diluted with water (45 c.c.) and shaken vigorously, the aqueous layer separated, and amyl alcohol removed in steam. The residual amine was distilled from a bath at 160—170° with superheated steam. Distillation was fairly rapid, the amine collecting in about 1 litre of distillate; this was extracted with ether, the extract dried (sodium sulphate), and the ether removed. The residue was distilled in a vacuum, the product collecting as a pale yellow oil which could not be induced to crystallise.

Reduction of 2-Amino-5-methylbenzophenone.—2-Amino-5-methylbenzophenone (4·8 g.) was reduced with sodium (4·8 g.) and *iso*amyl alcohol (48 c.c.) as above. The product was again a pale yellow oil (4·0 g.) which contained 62·0% of primary amine, *M* 197, hence 55·4% yield. The product gave a solid acetyl derivative, m. p. 164·5—165·5°, which was shown to be identical with 2-acetamido-5-methyldiphenylmethane (m. p. and mixed m. p.).

N-*Benzyl*-p-*toluidine.*—A mixture of *p*-toluidine (428 g.; 4 mols.), sodium hydrogen carbonate (105 g.; 1·25 mols.) and water (100 c.c.) was kept at 90—95°, and benzyl chloride (127 g.; 1 mol.) run in during 1½—2 hours with vigorous stirring. The hot mixture was filtered, the aqueous layer separated, and the oil washed with saturated salt solution. After drying (sodium sulphate), the mixture was distilled under reduced pressure, giving *p*-toluidine, b. p. 80—90°/12 mm., followed by *N*-benzyl-*p*-toluidine, b. p. 180—190°/12 mm. (148 g.; 75·1%). The latter formed a pale yellow oil which was employed in the migration experiments without further purification. The hydrochloride after one recrystallisation from alcohol–ether had m. p. 179—181° (Law, *J.*, 1912, **101**, 158, gives m. p. 181—182°).

2-Amino-5-methyldiphenylmethane.—The method described here is typical of all the benzyl rearrangements shown in the table below. The yields quoted in these experiments are based on an analytical method for primary amines supplied by Messrs. I.C.I., Ltd. (Dyestuffs Division), in which the diazotised amine is coupled with a standard solution of *p*-sulphophenylmethylpyrazolone.

A mixture of benzyl-*p*-toluidine (50 g.), *p*-toluidine (50 g.), and aluminium chloride (10 g.) was heated at 200° for 16 hours. The hot reaction mixture was poured into an excess of sodium hydroxide solution with stirring. Ether was added to assist the separation of the two layers. The mixture was filtered, and the ethereal layer separated and dried. After removal of the ether, the residue was fractionated, the two higher fractions being analysed for primary amine: Fraction I, up to 130°/12 mm., 22·6 g. of *p*-toluidine. Fraction II, 150—170°/0·1 mm., 23·0 g., 68·5% primary amine (*M*, 197). Fraction III, 165—200°/0·1 mm., 18·4 g., 48·7% primary amine (*M*, 197). Fraction IV, high-boiling residue, 21·7 g. Total yield of primary amine (*M*, 197) = 49·6%.

The *acetyl* derivative separated from alcohol as needles, m. p. 165·5° (Found: C, 80·4; H, 7·4. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2%). The p-*nitrobenzylidene* derivative separated from alcohol as yellow needles, m. p. 119° (Found: C, 76·8; H, 5·4; N, 8·5. $C_{21}H_{18}O_2N_2$ requires C, 76·4; H, 5·5; N, 8·5%).

Rearrangement of N-*benzyl*-p-*toluidine at* 200°.

(25 G. used in each experiment.)

Expt. No.	Catalyst.	Free base added.	Time (hrs.).	Yield (%).
I	$CoCl_2$, 10 g.	—	16	23·9
II	$AlCl_3$, 5 g.	—	16	25·1
III	$ZnCl_2$, 5 g.	—	16	12·8
IV	$CoCl_2$, 10 g.	*p*-Toluidine, 25 g.	17	1·5
V	$AlCl_3$, 5 g.	*p*-Toluidine, 25 g.	17	51·0
VI	$AlCl_3$, 5 g.	*p*-Toluidine, 50 g.	35	24·6

N-*Benzyl*-p-*chloroaniline.*—A mixture of *p*-chloroaniline (245·7 g.; 1·9 mols.), sodium hydrogen carbonate (105 g.; 1·25 mols.), and water (150 c.c.) was kept at 90—95°, and benzyl chloride (127 g.; 1 mol.) run in during 1 hour with vigorous stirring which was continued for a further 3 hours. The hot mixture was filtered, the aqueous layer separated, and the oil washed with saturated salt solution. Ether was added, and the ethereal solution dried (Na_2SO_4). The ether was removed, and the mixture distilled under reduced pressure, giving *p*-chloroaniline (126 g.), b. p. 120—135°/12 mm., followed by N-*benzyl*-p-*chloroaniline*, b. p. 207°/12 mm. (193 g.; 89%), m. p. 44°; after crystallisation from aqueous alcohol it had m. p. 45° (Found: C, 72·1; H, 5·8. $C_{13}H_{12}NCl$ requires C, 71·7; H, 5·5%).

5-Chloro-2-aminodiphenylmethane.—A mixture of benzyl-*p*-chloroaniline (185 g.), *p*-chloroaniline (126·1 g.), and aluminium chloride (38 g.) was heated at 200° for 15 hours. The reaction mixture was allowed to cool and while still fluid was poured into excess of sodium hydroxide solution with stirring. Ether was added, and the ethereal layer separated and dried (Na_2SO_4). The ether was removed, and the residue fractionated: Fraction I, up to 140°/12 mm., *p*-chloroaniline (83·5 g.). Fraction II, 145—190°/0·1 mm., brown liquid (104·1 g.). Fraction III, b. p. 190—225/0·1 mm., yellow crystalline solid (31 g.). There was a considerable tarry distillation residue (45 g.). Fraction II consisted essentially of 5-chloro-2-aminodiphenylmethane, which on redistillation through a fractionating column was obtained as a slightly brownish liquid, b. p. 140—145°/0·1 mm. (69 g.; 37%). It readily gave a *hydrochloride*, separating from dilute hydrochloric acid in colourless needles, m. p. 183—184° (Found: C, 61·2; H, 5·5; N, 5·8. $C_{13}H_{13}NCl_2$ requires C, 61·4; H, 5·2; N, 5·5%). Fraction III recrystallised once from alcohol and then several times from ethyl acetate formed yellow needles, m. p. 258—260° (Found: C, 70·7; H, 3·7; N, 4·5; Cl, 21·3. $C_{13}H_{12}NCl_2$ requires C, 70·9; H, 3·9; N, 4·3; Cl, 21·8%). This material is probably a *dihydroacridine* derivative of structure (V).

N-α-*Naphthylmethyl*-p-*toluidine*.—A 2-litre, three-necked flask was fitted with stirrer, condenser, and dropping-funnel. In the flask were placed *p*-toluidine (214 g.; 2 mols.), sodium hydrogen carbonate (126 g.; 1·5 mols.), and water (300 c.c.), and the whole heated on a steam-bath. 1-Chloromethylnaphthalene (160 g.; 0·9 mol.), dissolved in the minimum amount of benzene, was run in during 1 hour with vigorous stirring. The reaction was completed by heating on the steam-bath for a further 3 hours with stirring. After the mixture had been allowed to cool, ether was added, and the organic layer separated, dried (Na_2SO_4), and distilled. After a first fraction of unchanged *p*-toluidine (118·4 g.), N-α-*naphthylmethyl*-p-*toluidine* (200 g.; 89·5%) distilled at 185—200°/10^{-4} mm. It had m. p. 64—65° (Found: C, 86·6; H, 7·2. $C_{18}H_{17}N$ requires C, 87·4; H, 6·9%). The compound oxidised slowly on standing in air.

4-*Amino*-m-*tolyl*-α-*naphthylmethane*.—*N*-α-Naphthylmethyl-*p*-toluidine (200 g.; 0·8 mol.), *p*-toluidine (160 g.; 1·5 mols.), and aluminium chloride (40 g.) were heated at 200° for 8 hours with stirring. The product was made alkaline with sodium hydroxide whilst hot, cooled, and ether-extracted. The combined extracts were dried (Na_2SO_4) and distilled, yielding 4-*amino*-m-*tolyl*-α-*naphthylmethane* (135 g.; 67·5%), b. p. 190°/10^{-3} mm. Recrystallised from alcohol it formed colourless needles, m. p. 88° (Found: C, 87·6; H, 6·4. $C_{18}H_{17}N$ requires C, 87·4; H, 6·9%). The *acetyl* derivative separated from aqueous alcohol as colourless needles, m. p. 147·5° (Found: C, 83·0; H, 6·4. $C_{20}H_{19}ON$ requires C, 83·0; H, 6·6%).

5-*Methyldiphenylmethane*-2-*arsonic Acid*.—A suspension of 2-amino-5-methyldiphenylmethane hydrochloride (23·4 g.; 0·1 mol.) in dilute hydrochloric acid (21 c.c., *d* 1·18; 180 c.c. water) was cooled to − 5° and diazotised with a solution of sodium nitrite (6·9 g.) in water (15 c.c.) added during 2 hours. The mixture was filtered, and the filtrate diluted with water (total volume 250 c.c.). A second solution of arsenious oxide (19·8 g.), sodium hydroxide (12 g.), and sodium carbonate (15 g.) in water (total volume 250 c.c.) was prepared. The two solutions (cooled to 0°) were run simultaneously into a mixture of crushed ice (75 g.) and ammoniacal copper sulphate solution (13 c.c.; 10%) during 1 hour, the mixture being stirred and the temperature kept below 5° throughout. The rate of addition of the two solutions was so controlled that the arsenite solution was 10 c.c. in advance of the diazonium solution.

When the addition was complete, stirring was continued until the mixture failed to give a coloration with an alkaline solution of H-acid (approx. 15 minutes). After the addition of "filtercel" (10 g.), the mixture was filtered, and the filtrate carefully neutralised to litmus by the addition of dilute hydrochloric acid. The small precipitate was removed, and the filtrate acidified to Congo-red by addition of concentrated hydrochloric acid. 5-*Methyldiphenylmethane*-2-*arsonic acid* (11·1 g.; 51%) was collected, washed with water, and dried. After crystallisation from glacial acetic acid, it had m. p. 178—179° (Found: C, 55·1; H, 5·2. $C_{14}H_{15}O_3As$ requires C, 54·9; H, 4·9%).

3-*Methylarsacridinic Acid*.—A solution of 5-methyldiphenylmethane-2-arsonic acid (10·6 g.) in concentrated sulphuric acid (40 c.c.) was kept at 100° for 5 minutes. The mixture was poured into water (600 c.c.), and the precipitated crude arsinic acid purified by solution in hot aqueous sodium carbonate (charcoal/filtercel) and careful acidification of the filtrate with dilute hydrochloric acid. A repetition of this process yielded the arsinic acid as a solid, m. p. 184° (decomp.).

10-*Chloro*-3-*methyl*-5 : 10-*dihydroarsacridine*.—A suspension of 3-methylarsacridinic acid (4·0 g.) in a mixture of hydrochloric acid (50 c.c., *d* 1·18) and chloroform (50 c.c.) was treated with a rapid stream of sulphur dioxide for 5 minutes. A crystal of potassium iodide was added, and the boiling solution again treated with sulphur dioxide for 2 hours. After cooling, the chloroform layer was dried, the solvent removed, and the residue distilled under reduced pressure. The distillate crystallised from benzene–light petroleum, giving 10-*chloro*-3-*methyl*-5 : 10-*dihydroarsacridine*, m. p. 87° (Found: C, 57·2; H, 4·2; $C_{14}H_{12}ClAs$ requires C, 57·8; H, 4·1%).

5-*Chlorodiphenylmethane*-2-*arsonic Acid*.—5-Chloro-2-aminodiphenylmethane hydrochloride (25·4 g., 0·1 mol.) was diazotised as for the 5-methyl compound (see above), being filtered and diluted after 20 mins. A second solution of arsenious oxide (19·8 g.; 0·2 equiv.) and sodium carbonate (15·9 g.; 0·3 equiv.) in water (total volume 250 c.c.) was prepared, and the procedure was continued as before, but at ½ hour intervals 5 g. quantities of calcium carbonate were added to the batch to improve the condition of the tar formed in the reaction. When the addition was complete, the product was worked up as above. 5-*Chlorodiphenylmethane*-2-*arsonic acid* (7·05 g.; 21·8%) was collected, washed with water and dried. After crystallisation from aqueous "cellosolve" it had m. p. 189° (Found: C, 48·4; H, 4·0. $C_{13}H_{12}O_3ClAs$ requires C, 47·8; H, 3·7%).

3-*Chloroarsacridinic Acid*.—A solution of 5-chlorodiphenylmethane-2-arsonic acid (5 g.) in concentrated sulphuric acid (17·9 c.c.) was kept at 100° for 5 minutes. The mixture was poured into water (200 c.c.) with stirring. The product soon crystallised and was collected, washed, and dried at 60° for 16 hours. The 3-*chloroarsacridinic acid* (4·2 g.; 88·5%) after crystallisation from aqueous acetic acid formed colourless needles, m. p. 210—212° (decomp.) (Found: C, 50·9; H, 3·6. $C_{13}H_{10}O_3ClAs$ requires C, 50·6; H, 3·2%).

3 : 10-*Dichloro*-5 : 10-*dihydroarsacridine*.—A suspension of 3-chloroarsacridinic acid (3·9 g.) in a mixture of hydrochloric acid (45 c.c., *d* 1·18) and chloroform (45 c.c.) was treated as above. After removal of the chloroform, the product crystallised on trituration with ether; after recrystallisation from benzene–light petroleum 3 : 10-*dichloro*-5 : 10-*dihydroarsacridine* (3·87 g.; 98·2%) was obtained as colourless needles, m. p. 116° (Found: C, 49·9; H, 2·9. $C_{13}H_9Cl_2As$ requires C, 50·2; H, 2·9%).

3-*Chloro*-10-*cyano*-5 : 10-*dihydroarsacridine*.—2 : 5-Dichloro-5 : 10-dihydroarsacridine (2·12 g.) was added to potassium cyanide (0·445 g.) dissolved in absolute methanol (7 c.c.). The mixture was refluxed for 20 minutes, filtered hot, and allowed to cool. The filtrate deposited colourless crystals of 3-*chloro*-10-*cyano*-5 : 10-*dihydroarsacridine* (1·105 g.; 49%). Recrystallised from anhydrous methanol, the product had m. p. 113—114° (Found: C, 55·7; H, 3·2; N, 4·4. $C_{14}H_8NClAs$ requires C, 55·7; H, 3·0; N, 4·7%). The compound appeared to hydrolyse rather readily when heated with aqueous solvents.

5-*Nitro*-2-*acetamidodiphenylmethane*.—2-Acetamidodiphenylmethane (40 g.) in glacial acetic acid

(30 c.c.) and concentrated sulphuric acid (80 c.c.) was cooled to − 5°, and nitric acid (8 c.c., *d* 1·5) in glacial acetic acid (25 c.c.) was added dropwise with stirring. The temperature was kept below − 5° throughout. After a further 2 hours' stirring, the reaction mixture was poured on ice, diluted with water, and left overnight. On crystallisation from acetone the *product* separated as colourless needles, m. p. 200° (yield, 41 g.; 86%) (Found: C, 66·7; H, 5·0; N, 10·7. $C_{15}H_{14}O_5N_2$ requires C, 66·7; H, 5·2; N, 10·4%).

5-Nitro-2-aminodiphenylmethane.—5-Nitro-2-acetamidodiphenylmethane (27·0 g.) was refluxed with concentrated hydrochloric acid (250 c.c.) and glacial acetic acid (50 c.c.) for 6 hours, and the mixture poured into excess of aqueous sodium hydroxide solution; the *product* was filtered off, washed, and recrystallised several times from alcohol, forming yellow prisms, m. p. 104—105° (yield, 16·0 g.; 70%) (Found: C, 68·8; H, 5·5; N, 12·1. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

Our thanks are due to the Chief Scientist, Ministry of Supply, for permission to publish these results.

THE UNIVERSITY, MANCHESTER. [*Received, April 21st,* 1947.]

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75. *Anhydrides of Polyhydric Alcohols. Part X. The Conversion of Glucamine into* 1 : 4-*Anhydrosorbitol. The Constitution of Benzylidene* 1 : 4-*Anhydrosorbitol.*

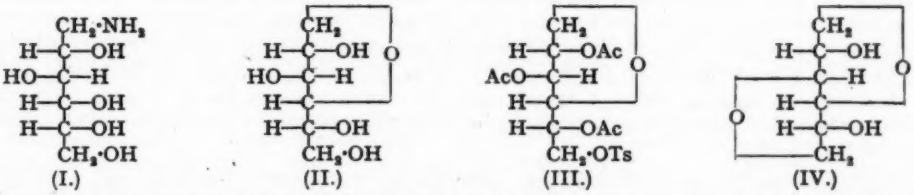
By V. G. BASHFORD and L. F. WIGGINS.

1 : 4-Anhydrosorbitol has been obtained by the deamination of glucamine. Its structure is discussed, and a benzylidene derivative is proved to be 3 : 5-benzylidene 1 : 4-anhydrosorbitol.

THE deamination of glucosamine leads to the formation of the anhydro-sugar, chitose, which almost certainly has a hydroxylated tetrahydrofuran structure. The deamination is accompanied by Walden inversion, since the 2 : 5-anhydro-compound has been shown by Levene (*J. Biol. Chem.*, 1924, **59**, 135) to possess the mannose configuration. More recently it has been shown that 2-amino 4 : 6-benzylidene α-methylaltroside undergoes Walden inversion and concomitant anhydro-ring formation on deamination to yield 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (Wiggins, *Nature*, 1944, **157**, 300). As a result of this observation it was anticipated that the deamination of glucamine (1-amino sorbitol), produced by the catalytic hydrogenation of glucose in the presence of ammonia (Adkins and Wayne, *J. Amer. Chem. Soc.*, 1940, **62**, 3314), would also result in the formation of an anhydro-ring. Since the amino-group is attached to C_1, and is therefore free to rotate, it was also expected that this anhydro-ring formation would take place without Walden inversion.

This prediction has now been verified, since treatment of glucamine (I) with nitrous acid has been shown to give a crystalline compound identical with that obtained by the restricted anhydridisation of sorbitol in the presence of sulphuric acid (Soltzberg, Goepp, and Freudenberg, *J. Amer. Chem. Soc.*, 1946, **68**, 919) which Hockett, Conley, Yusem, and Mason (*ibid.*, p. 922) have shown, by a study of its behaviour towards lead tetra-acetate, to be 1 : 4-anhydrosorbitol (II).

It is apparent therefore that there is now available a new method for the introduction of anhydro-rings into the polyhydric alcohols derived from sugars.



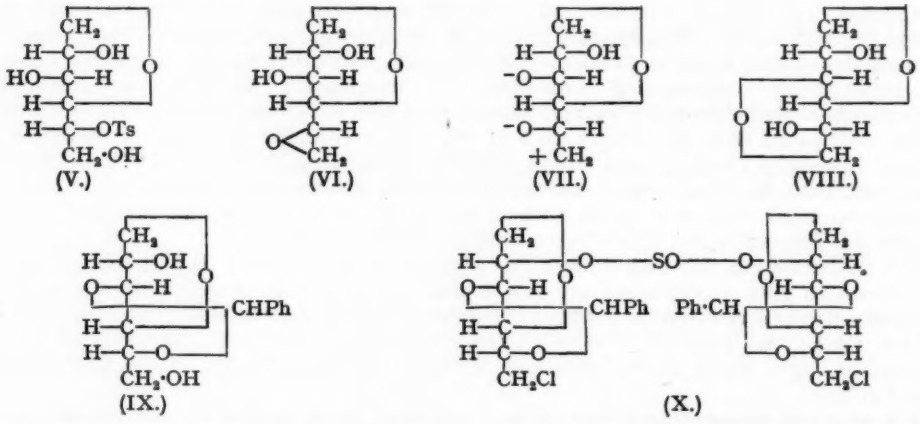
(I.) (II.) (III.) (IV.)

Proof, additional to that of Soltzberg, Goepp, and Freudenberg (*loc. cit.*), that this is indeed 1 : 4-anhydrosorbitol would be afforded if it could be converted into the dianhydride, *iso*sorbide, since this has been shown unequivocally to be 1 : 4-3 : 6-dianhydrosorbitol (IV) (Montgomery and Wiggins, *Nature*, 1946, **157**, 372; *J.*, 1946, 390; Hockett, Fletcher, Sheffield, and Goepp, *J. Amer. Chem. Soc.*, 1946, **68**, 927). This conversion has now been effected in the following way. The anhydrosorbitol obtained on the deamination of glucamine gave, on selective tosylation followed by acetylation, liquid 6-tosyl 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol (III). The presence of a tosyl group at either C_1 or C_6 was proved by the observation that treatment of

(III) with sodium iodide in acetone at 100° afforded a 90% yield of sodium *p*-toluenesulphonate. Treatment of (III) with four mols. of sodium in methyl alcohol effected simultaneous deacetylation and anhydro-ring formation with the production of 1 : 4-3 : 6-dianhydrosorbitol (IV), recognised by its conversion into the characteristic crystalline 2 : 5-*bismethanesulphonyl* 1 : 4-3 : 6-*dianhydrosorbitol*. The isolation of the latter proves that the anhydrosorbitol must be either 1 : 4- or 3 : 6-anhydrosorbitol. Since the 3 : 6-anhydro-derivative has been previously prepared by Fischer and Zach (*Ber.*, 1912, **45**, 2069) and has constants different from those of the anhydride under discussion, it is clear that the latter must contain the 1 : 4-anhydro-ring. The structure (II) assigned to the anhydrosorbitol obtained by the deamination of glucamine or by the restricted dehydration of sorbitol is therefore correct.

The action of methanesulphonyl chloride on the product of detosylation and deacetylation of 6-tosyl triacetyl 1 : 4-anhydrosorbitol gave, in addition to 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol, 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol (VIII) (Wiggins, *Nature*, 1947, **157**, 372), as well as a methanesulphonyl derivative, m. p. 82—83°, not yet identified. The formation of (VIII) lends support to the view that the anhydrosorbitol obtained by deamination of glucamine is indeed (II).

The isolation of a derivative of 1 : 4-3 : 6-dianhydro-L-iditol is of interest not only from the constitutional point of view but also from its mode of formation; the following represents one possible mechanism. Tosylation of 1 : 4-anhydrosorbitol probably gives some 5-tosyl 1 : 4-anhydrosorbitol (V) in addition to the 6-tosyl isomer which must be the main product. Detosylation of the 5-tosyl isomer (V) might then give rise to 1 : 4-5 : 6-dianhydro-L-iditol (VI); that is to say, the removal of the tosyl group at C_5 would be accompanied by Walden inversion. Rearrangement of this product through (VII) as a possible intermediate could then give the more stable bicyclic structure, 1 : 4-3 : 6-dianhydro-L-iditol (VIII).



In seeking to obtain characteristic derivatives of 1 : 4-anhydrosorbitol we obtained crystalline 2 : 3 : 5 : 6-*tetrakismethanesulphonyl* 1 : 4-*anhydrosorbitol*, liquid 2 : 3 : 5 : 6-*tetra-acety* 1 : 4-*anhydrosorbitol*, and a crystalline monobenzylidene 1 : 4-anhydrosorbitol of m. p. 154—155° and $[\alpha]_D$ + 15·4° which appears to be different from the monobenzylidene derivatives {(*a*) m. p. 136—140°, $[\alpha]_D$ − 33·7°; (*b*) m. p. 121—122°, no $[\alpha]_D$ recorded} obtained by Soltzberg, Goepp, and Freudenberg (*loc. cit.*) by a different method. Thus (*a*) may be an impure form of the compound described herein, which is shown to be 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* (IX) by the following facts.

Ultimate analysis gave results in agreement with those required by benzylidene 1 : 4-anhydrosorbitol. On treament of its *monotosyl* derivative with sodium iodide in acetone at 100°, sodium *p*-toluenesulphonate was isolated (90% yield). Thus the original monobenzylidene 1 : 4-anhydrosorbitol must have an unsubstituted hydroxyl at C_6. It was also found that this 6-tosyl derivative was stable to cold sodium methoxide. Since a 6-tosyl compound possessing a hydroxyl group adjacent to the tosyl residue would readily afford a 5 : 6-ethylene oxide anhydro-ring, it is concluded that the hydroxyl group at C_5 is engaged in union with the benzylidene group. It follows therefore that this must engage either $C_3 : C_5$ or $C_3 : C_5$. A study of models shows that of the two possibilities the former is sterically highly unlikely. The tentative conlusion is therefore reached that the benzylidene group engages

C_3 and C_5 as in (IX). Confirmation of this structure is provided through the product of chlorination of the monobenzylidene 1 : 4-anhydrosorbitol. This was identical with that obtained by chlorination of 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol, the structure of which has been established (see Part IX, this vol., p. 237).

The 3 : 5-benzylidene derivative of 1 : 4-anhydrosorbitol provides a means whereby a more selective tosylation at C_6 can be made to take place; thus we have prepared crystalline *6-tosyl* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*, in which the tosyl group is readily exchanged for iodine giving *6-iodo* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*. The tosyl compound on debenzylidenation gave liquid 6-tosyl 1 : 4-anhydrosorbitol, which after detosylation with sodium methoxide gave mainly 1 : 4-3 : 6-dianhydrosorbitol, isolated as its bismethanesulphonyl derivative, together with the unknown methanesulphonyl compound, m. p. 82—83°. No derivative of dianhydro-L-iditol was isolated.

Treatment of 3 : 5-benzylidene 1 : 4-anhydrosorbitol with thionyl chloride and pyridine would be expected to yield 2 : 6-dichloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol; in fact, however, the product (m. p. 108—109°) contained only one chlorine atom per molecule of sorbitol and also contained sulphur and combined benzaldehyde; moreover, its molecular weight showed it to be bimolecular with respect to 1 : 4-anhydrosorbitol. This product was hydrolysed to 6-chloro 1 : 4-anhydrosorbitol. It was also obtained from thionyl chloride, pyridine, and 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (see Part IX, *loc. cit.*), in which the C_2 is the only position available for substitution. For these reasons it is tentatively suggested that the product is *bis*-(6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*) 2 : 2′-*sulphite* (X).

Experimental.

Deamination of Glucamine.—Glucamine (Adkins and Wayne, *loc. cit.*) (10 g.) was dissolved in water and the solution acidified with glacial acetic acid. Sodium nitrite (4·7 g.) was then added in small portions. The solution was well stirred and then left at room temperature overnight; thereafter it was neutralised with sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residue was extracted with dry ethyl acetate in a Soxhlet apparatus. On standing, crystals of 1 : 4-anhydrosorbitol were formed and were recrystallised from ethyl alcohol–ethyl acetate. Yield, 5·15 g.; m. p. 114—116°, $[\alpha]_D^{15°}$ — 22·21° (*c*, 1·5 in water). Soltzberg, Goepp, and Freudenberg (*loc. cit.*) described 1 : 4-anhydrosorbitol as having m. p. 115—116°, $[\alpha]_D$ — 21·9°.

2 : 3 : 5 : 6-*Tetra-acetyl* 1 : 4-*Anhydrosorbitol.*—(*a*) 1 : 4-Anhydrosorbitol (0·4 g.) was dissolved in dry pyridine, acetic anhydride (2·0 c.c.) added, and the mixture kept at room temperature for 4 days. The solution was then poured into ice–water and extracted with chloroform. The chloroform extracts were washed with N-sulphuric acid, sodium hydrogen carbonate solution, and twice with water, dried ($MgSO_4$), and evaporated to dryness. The residue of 2 : 3 : 5 : 6-*tetra-acetyl* 1 : 4-*anhydrosorbitol* distilled at 195—200° (bath temp.)/0·01 mm. as a colourless liquid (0·604 g.), $n_D^{15°}$ 1·4549, $[\alpha]_D^{14·5°}$ + 46·4° (*c*, 2·995 in chloroform).

(*b*) 1 : 4-Anhydrosorbitol (0·59 g.), fused sodium acetate (0·6 g.), and acetic anhydride were refluxed for 1½ hours and the mixture poured into ice–water. The solution was neutralised with sodium hydrogen carbonate and extracted several times with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue distilled at 195—200° (bath temp.)/0·01 mm. as a colourless syrup (1·228 g.), $n_D^{20°}$ 1·4559, $[\alpha]_D^{16°}$ + 47·6° (*c*, 2·395 in chloroform) (Found : C, 50·7; H, 6·6; Ac, 51·2. $C_{14}H_{20}O_9$ requires C, 50·6; H, 6·0; Ac, 51·8%).

2 : 3 : 5 : 6-*Tetrakismethanesulphonyl* 1 : 4-*Anhydrosorbitol.*—1 : 4-Anhydrosorbitol (0·103 g.) and methanesulphonyl chloride (0·3 c.c.) were mixed in dry pyridine (5·0 c.c.) and kept at room temperature for 3 days. The mixture was poured into ice–water and the aqueous solution extracted several times with chloroform, and the combined extracts dried ($MgSO_4$) and evaporated to dryness. The residue crystallised after treatment with acetone–ethyl alcohol. The *compound* (0·17 g.) recrystallised from the same solvents and showed m. p. 122°. Further recrystallisation raised the m. p. to 122·5°, $[\alpha]_D^{19·5°}$ — 3·46° (*c*, 2·3 in acetone) (Found : C, 25·7; H, 4·5. $C_{10}H_{20}O_{13}S_4$ requires C, 25·2; H, 4·2%).

3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—1 : 4-Anhydrosorbitol (5·0 g.), benzaldehyde (redistilled, 25 c.c.), and anhydrous finely-ground zinc chloride (6·0 g.) were shaken for 16 hours. Sodium carbonate (12·0 g.), dissolved in water, was added to the mixture which was then evaporated to dryness. The residue was extracted with chloroform in a Soxhlet apparatus, and the chloroform solution dried ($MgSO_4$) and evaporated under reduced pressure. The crystals of 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* which separated were triturated with ether, collected, and recrystallised from alcohol–light petroleum. Yield, 1·78 g., m. p. 154—155°, $[\alpha]_D^{19°}$ + 15·4 (*c*, 3·9 in acetone). A further crop (0·45 g.) was obtained from the mother liquors (Found : C, 62·6; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%).

6-*Tosyl* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—To a solution of 3 : 5-benzylidene 1 : 4-anhydrosorbitol (1·679 g.) in dry pyridine (10 c.c.) cooled to 0°, *p*-toluenesulphonyl chloride (1·395 g.) was added gradually with shaking, and the solution was left at room temperature for 2 days and then poured into ice–water. A white solid was deposited which was filtered off, washed with water, and recrystallised from alcohol–water. 6-*Tosyl* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* had m. p. 125·5°, $[\alpha]_D^{23°}$ + 9·1° (*c*, 2·2 in chloroform). Yield, 0·86 g. (Found : C, 59·2; H, 5·6. $C_{20}H_{22}O_7S$ requires C, 59·2; H, 5·4%).

Bis-(6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol*) 2 : 2′-*Sulphite.*—3 : 5-Benzylidene 1 : 4-anhydrosorbitol (0·5 g.), thionyl chloride (0·36 c.c.), and dry pyridine (1·5 c.c.) were mixed and left at 0° for ½ hour. The solution was then brought to room temperature, anhydrous magnesium sulphate (0·1 g.) added, and the whole heated on the water-bath for 45 minutes; the mixture was then cooled and poured into

ice–water. After trituration the solid was filtered off and recrystallised from alcohol–water. Yield, 0·2 g.; m. p. 96—98°. On further recrystallisation from alcohol, the *compound* had m. p. 106—107°, alone or in admixture with the product obtained on similar treatment of 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (see Part IX, *loc. cit.*); $[\alpha]_D^{16\cdot2°}$ + 46·8° (*c*, 2·2 in chloroform) [Found: C, 53·2; H, 5·1; Cl, 13·5; S, 5·8; *M* (Rast), 550. $C_{16}H_{19}O_5Cl_2S$ requires C, 53·2; H, 4·8; Cl, 12·1; S, 5·5%; *M*, 582].

The compound (0·98 g.) in acetone (40 c.c.) was heated under reflux with oxalic acid (1·5 g.) in water (5 c.c.) for 18 hours. The acid was neutralised with barium carbonate, and the solution filtered and evaporated to dryness. The dry residue was extracted several times with boiling chloroform. On standing, the chloroform extracts deposited crystals (0·26 g.) which had m. p. 108—109° alone or in admixture with 6-chloro 1 : 4-anhydrosorbitol (see Part IX, *loc. cit.*). It showed $[\alpha]_D$ − 13·8° (*c*, 2·33 in acetone) in agreement with that previously recorded. The chloroform mother liquors deposited a further amount of the same material (0·06 g.) on evaporation.

6-Iodo 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—A solution of 6-tosyl 3 : 5-benzylidene 1 : 4-anhydrosorbitol (0·5 g.) and dry sodium iodide (0·75 g.) in dry acetone (50 c.c.) was heated in a sealed tube at 110° for 4 hours. Crystals of sodium *p*-toluenesulphonate separated during the reaction. When the tube had cooled these crystals were filtered off. Yield, 0·23 g. (89·9%). The acetone filtrate was evaporated and the residue extracted with chloroform. The chloroform was dried ($MgSO_4$) and concentrated, and the crystals of *6-iodo* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* were filtered off and washed with ether; m. p. 144° (Found: C, 42·7; H, 4·5. $C_{13}H_{15}O_4I$ requires C, 43·2; H, 4·2%).

6-Tosyl 1 : 4-*Anhydrosorbitol.*—6-Tosyl 3 : 5-benzylidene 1 : 4-anhydrosorbitol (6·68 g.), oxalic acid (10·0 g.), water (31·0 c.c.) and acetone (250 c.c.) were refluxed for 18 hours, during which $[\alpha]_D$ changed from + 5·05° to + 13·46°. The solution was cooled and neutralised with barium carbonate. The insoluble salts were removed by centrifuging and the remaining clear solution evaporated to dryness under reduced pressure. The residue was extracted with chloroform and the chloroform extracts evaporated; the *compound* was a syrup which failed to crystallise. Yield, 3·07 g., $[\alpha]_D^{17\cdot8°}$ + 10·5 (*c*, 2·095 in chloroform) (Found: S, 10·3. $C_{13}H_{18}O_7S$ requires S, 10·05%).

2 : 5-*Bismethanesulphonyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—1 : 4-3 : 6-Dianhydrosorbitol (10 g.) was dissolved in dry pyridine (50 c.c.), and methanesulphonyl chloride (23 g.) added slowly at 0° with occasional shaking. Thereafter the mixture was kept overnight and then poured into ice–water. The precipitated *bismethanesulphonyl* derivative, after being collected and washed with water, was recrystallised from alcohol; m. p. 122—123°, $[\alpha]_D$ + 77·7° (*c*, 1·416 in chloroform) (Found: C, 31·9; H, 4·6. $C_8H_{14}O_8S_2$ requires C, 31·8; H, 4·7%).

Action of Sodium Methoxide on 6-*Tosyl* 1 : 4-*Anhydrosorbitol.*—6-Tosyl 1 : 4-anhydrosorbitol (3·06 g.) was dissolved in chloroform and cooled to 0°. Sodium (0·24 g.) was dissolved in dry methanol and cooled to 0°. The two solutions were mixed and left overnight at room temperature. More chloroform was added and the solution extracted with water. The combined aqueous extracts were neutralised with N-sulphuric acid and evaporated to dryness in the presence of barium carbonate (1·0 g.). The residue was extracted 3 times with hot ethyl acetate and the extracts evaporated to dryness under reduced pressure. The resulting syrup (1·527 g.) was dried, dissolved in dry pyridine at 0°, methanesulphonyl chloride (3·4 c.c.) added, and the solution left at room temperature overnight. The solution was then poured into water, and a flocculent precipitate and a gum were deposited. The precipitate was filtered off, dissolved in acetone, charcoaled, filtered off, and treated with ethyl alcohol; crystals (0·24 g.) of 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol were obtained, m. p. 123° alone or in admixture with an authentic specimen; $[\alpha]_D^{18°}$ + 78·5° (*c*, 1·412 in chloroform).

The gum was dissolved in chloroform and the chloroform solution washed with N-sulphuric acid, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The solution was evaporated to dryness and treated with acetone–ethyl alcohol, giving a compound, m. p. 82—83°, $[\alpha]_D$ + 25·1° (*c*, 2·215 in chloroform), which has not yet been identified.

Conversion of 1 : 4-*Anhydrosorbitol into the* 2 : 5-*Bismethanesulphonyl Derivatives of* 1 : 4-3 : 6-*Dianhydrosorbitol and of* 1 : 4-3 : 6-*Dianhydro-*L*-iditol.*—1 : 4-Anhydrosorbitol (1·0 g.) was dissolved in dry pyridine, cooled to 0°, and treated with *p*-toluenesulphonyl chloride (1·2 g.) with cooling and shaking. Thereafter it was left at room temperature for 52 hours. The solution was then cooled again to 0° and acetic anhydride (4·6 c.c.) added, and the mixture left at room temperature for 48 hours. The solution was then poured on ice–water and the deposited oil extracted with chloroform. The chloroform extracts were washed with N-sulphuric acid, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated to dryness. The resulting syrup (2·095 g.) was mainly 6-tosyl 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol, contaminated with the corresponding 5-tosyl derivative. It had $[\alpha]_D^{16\cdot5°}$ + 25·3° (*c*, 1·2 in chloroform). To a solution of the syrup (1·99 g.) in chloroform, a solution of sodium (0·428 g.) in absolute methyl alcohol was added at 0° and the mixture kept at room temperature overnight. Thereafter more chloroform was added and the solution extracted several times with water. The aqueous extracts were neutralised with N-sulphuric acid and evaporated to dryness in the presence of barium carbonate (0·5 g.). The residue was extracted with chloroform and the chloroform solution evaporated to a syrup, which was distilled at 220° (bath temp.)/10 mm., and separated into two fractions: (i) 0·153 g., $n_D^{18°}$ 1·4982, $[\alpha]_D^{14°}$ + 18·4° (*c*, 5·1 in chloroform); (ii) 0·15 g., $n_D^{18°}$ 1·4982 ($[\alpha]_D$ could not be determined owing to opacity).

Both fractions were treated with methanesulphonyl chloride (0·4 c.c.) in dry pyridine at 0°. When the solution from (i) was poured into water a solid was obtained which, recrystallised from ethyl alcohol, had m. p. 109°. Two further recrystallisations raised the m. p. to 112°, and after several more recrystallisations a product was obtained (0·0107 g.) of m. p. 119—122°, $[\alpha]_D^{18°}$ + 71·0 (*c*, 0·5 in chloroform). This was doubtless impure 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol.

The mother liquors were evaporated to dryness and dissolved in acetone–ethyl alcohol, from which solution a few crystals of m. p. 155—156° were obtained together with some material, m. p. 82°. The former showed no depression of m. p. in admixture with 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydro-L-iditol, and had the identical $[\alpha]_D^{18°}$ + 41·4° (*c*, 1·98 in acetone). The material, m. p. 82°, was identical

with the compound of the same m. p. obtained by Montgomery and Wiggins (Part IX, *loc. cit.*) from the product of the action of sodium methoxide on 6-chloro 1 : 4-anhydrosorbitol. The solution from fraction (ii) was poured into water and the product extracted with chloroform. The chloroform extracts were washed with sulphuric acid, sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated to dryness. The residual syrup eventually crystallised and after two recrystallisations had m. p. 81—82°. As the amount of this compound was small (0·0043 g.) its optical rotation could not be determined. It was identical with the compound of the same m. p. obtained from fraction (i).

The mother liquors from the recrystallisation were combined and concentrated; crystals were obtained (0·018 g.) showing m. p. 122° (alone or in admixture with 2 : 5-bismethanesulphonyl dianhydrosorbitol) and $[\alpha]_D^{20°}$ + 80·85° (*c*, 0·94 in chloroform).

The experiment was repeated on a larger scale, with the same result.

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THE A.E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, April 10th*, 1947.]

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76. *Amidines. Part VIII. Preparation of Amidines from Cyanides, Ammonia or an Amine, and an Ammonium or Substituted-ammonium Salt.*

By P. OXLEY, M. W. PARTRIDGE, and W. F. SHORT.

Amidines and their *N*-substituted derivatives may be prepared by heating a cyanide, ammonia or a primary or secondary amine, and the corresponding ammonium or substituted-ammonium salt, especially a sulphonate, at a suitable temperature within the range 150—220°.

THE production of amidines by the addition of ammonia or an amine to a cyanide has been recorded with ethyl cyanotartronate (Curtis and Nickell, *J. Amer. Chem. Soc.*, 1913, **35**, 887) and trichloromethyl cyanide (I.G., G.P., 671,785), and the enhanced activity of the cyano-group in these compounds may be attributed to the inductive effect of the polar substituents (cf. Part I, *J.*, 1946, 147). It has been stated (Drew and Kelly, *J.*, 1941, 630) that a diamidine is formed by addition of ammonia to 3 : 6-dihydroxy-*o*-phenylene dicyanide, but it seemed unlikely that the cyano-group in this compound would be activated, and, moreover, the production of a diamidine would be opposed by the steric effect of the *o*-substituents. Mr. F. F. Whitmont has now shown that the compound produced from this cyano-phenol and cold alcoholic ammonia is in fact the diammonium salt and not 3 : 6-dihydroxyphthalodiamidine.

We have now shown that an equilibrium mixture containing approximately 1% of amidine is obtained by the decomposition of *p*-methylsulphonylbenzamidine at 180° or by heating *p*-methylsulphonylphenyl cyanide in an atmosphere of ammonia at this temperature. Amidines were also obtained in the yields shown in parentheses when this cyanide was heated at 180° with dimethylamine (0·7%), 2-aminopyridine (11%), or piperidine (24%). Similarly, phenyl cyanide and piperidine afforded *NN*-pentamethylenebenzamidine (1·5%) after 3 hours at 180°. Combination of cyanides with typical aromatic amines, such as aniline, has so far not been detected (see below). It seemed probable that by selecting a suitable reaction temperature many cyanides would combine with ammonia or amines to yield amidines but that only in exceptional cases would sufficient amidine be present at equilibrium to make the reaction of value as a method of preparation. Since amidines are usually stronger bases than ammonia or amines, it seemed probable that if the reaction were carried out in presence of an ammonium salt, an amidinium salt would be formed, and, provided that the temperature was lower than that at which this salt dissociates (Part I, *loc. cit.*), the equilibrium would be disturbed and conversion of the cyanide into the amidine would be promoted :

$$R{\cdot}CN + NHXY \longleftrightarrow R{\cdot}C(:NH){\cdot}NXY \xleftrightarrow{\overset{\oplus}{N}H_4XY} R{\cdot}C(:NH){\cdot}\overset{\oplus}{N}HXY + NHXY \quad . \quad . \quad (1)$$

In agreement with this conclusion, an 83% yield of *p*-methylsulphonylbenzamidinium benzenesulphonate was obtained when *p*-methylsulphonylphenyl cyanide and ammonium benzenesulphonate (1 mol.) were heated in an atmosphere of ammonia for 2½ hours at 180°, and a number of amidines and *N*-substituted amidines have been prepared in a similar manner. The reaction appears to be controlled by a number of factors, some of which act in opposition. Thus, although the presence of a more strongly anionoid nitrogen atom in the base would facilitate addition to the cyanide, this increase in the strength of the base would decrease the proportion of

amidine converted into salt, with a correspondingly smaller displacement of the equilibrium between the cyanide, base, and amidine (1). When dissociation of the amidinium salt takes place, the relative volatility of the base and of the amidine will have an influence on the reaction. Ammonium and substituted-ammonium sulphonates are preferably employed as salts owing to the stability of the corresponding amidinium sulphonates, but other salts, including chlorides and thiocyanates, have given satisfactory results in a number of cases. The relative efficiency of various salts also depends to some extent on their miscibility with the molten cyanide, and when solidification of the reaction mixture occurs owing to the separation of the amidinium salt, the reaction is impeded, especially when the base is a gas. The addition of a solvent was sometimes beneficial in these cases; for example, *p*-methylsulphonylbenzamidine was obtained in only 15% yield from the corresponding cyanide, ammonium chloride, and ammonia at 180°, and the addition of acetamide increased the yield to 43% under otherwise identical conditions. Urea and substituted ureas can be used as solvent and as a source of ammonia or amine. Thus, *p*-methylsulphonylbenzamidine (43%) was obtained from the cyanide, ammonium chloride, and urea at 180°, and *NN*-dimethyl-*p*-methylsulphonylbenzamidine (32%) was similarly obtained from the cyanide, *NN*-dimethylurea, and dimethylammonium chloride.

It must be emphasized that reaction (1) is quite distinct from that which takes place between a cyanide and an ammonium sulphonate (Part I, *loc. cit.*; Part VII, *J.*, 1947, 1110):

$$R\cdot CN + \overset{\oplus}{N}H_2XY\}Ar\cdot\overset{\ominus}{S}O_3 \longleftrightarrow R\cdot C(:NH)\overset{\oplus}{N}HXY\}Ar\cdot\overset{\ominus}{S}O_3 \quad . \quad . \quad . \quad . \quad (2)$$

Thus, when arylammonium salts are used in reaction (2) good yields of amidinium salts are obtained, but, under the same conditions, cyanides do not add arylamines to yield free *N*-arylamidines, in spite of the fact that these amidines are stable at the temperature employed. For example, although *N*-phenyl-*p*-methylsulphonylbenzamidine suffered no appreciable decomposition when heated at 180° for 3 hours, no detectable quantity of this amidine was formed from *p*-methylsulphonylphenyl cyanide and aniline under these conditions, but the use of anilinium benzenesulphonate in place of aniline gave an 86·5% yield of the amidinium benzenesulphonate. Similarly, although Bernthsen (*Annalen*, 1877, **184**, 341; 1878, **192**, 4) found that phenyl cyanide does not react with aniline or diphenylamine at 280—360°, yet *N*-phenyl- and *NN*-diphenyl-benzamidinium salts are readily prepared by using phenyl- and diphenyl-ammonium salts respectively (see Part I, *loc. cit.*). We found that trichloromethyl cyanide did not react with aniline in benzene solution under conditions which, as stated by the I.G. (*loc. cit.*), give an almost quantitative yield of trichloroacetamidine when ammonia is used in place of aniline. A further distinction between the reactions is observed in the case of *o*-substituted phenyl cyanides which afford very poor yields in reaction (1) but moderately good yields in reaction (2). Reaction (1) usually takes place at a considerably lower temperature. Thus, whereas *p*-methylsulphonylphenyl cyanide and ammonium benzenesulphonate (1 mol.) afforded traces of amidinium salt after 2½ hours at 180°, *ca.* 3% after 2 hours at 220°, and 61% after 2 hours at 250°, an 83% yield was obtained in 2½ hours at 180° in the presence of ammonia. Our rejection of the hypothesis that reaction (2) involves dissociation of the ammonium salt (Part I, *loc. cit.*) is therefore now supported by further evidence.

In an inconclusive attempt to obtain additional evidence that reaction (1) does in fact involve the addition of ammonia or an amine to the cyanide and not simply its reaction with the ammonium salt, it was found that *p*-methylsulphonylbenzamidine and its *NN*-dimethyl derivative were both produced when *p*-methylsulphonylphenyl cyanide was heated either with ammonia and dimethylammonium benzenesulphonate or with dimethylamine and ammonium benzenesulphonate. The influence of experimental conditions on the ratio of the two amidines formed indicated that the controlling factors are the relative strengths of the four bases concerned and the stability of the free amidines. For example, when the cyanide and ammonium benzenesulphonate (1 mol.) were heated at 180° for 3 hours in a slow stream of dimethylamine, *p*-methylsulphonylbenzamidine and its *NN*-dimethyl derivative were produced in 0·03 and 79% yield, respectively. Under the same conditions, the cyanide, dimethylammonium benzenesulphonate, and ammonia afforded 62% of the unsubstituted amidine and 17% of the *NN*-dimethylamidine, but when the amount of ammonia was limited to 1 mol., the volume of the gas phase decreased by 27% and the yields of unsubstituted and substituted amidine were 32 and 52%, respectively. The decrease in the volume of gas would be accounted for if the substituted amidine and dimethylamine have approximately the same basic strength, so that some of the amidine is displaced from its salt by the amine.

During the preparation of amidines by heating cyanides with ammonium thiocyanate (Part

IV, *J.*, 1947, 390) ammonia is freely evolved, and it is probable that a reaction analogous to reaction (1) takes place. Many cyanides appear to react more readily with ammonium thiocyanate than with ammonia in presence of an ammonium salt and, although this may be due solely to physical factors, it is possible that a reaction of type (2) takes place simultaneously.

Experimental.

Note.—The yields of amidines recorded are not necessarily the highest obtainable since a systematic examination of the effect of conditions on the yield of amidine was not made in all cases. Detailed descriptions of the isolation of the amidines are given in special cases only, since the methods employed followed closely those described in previous parts of this series, to which reference is made for earlier descriptions of many of the amidines (Part I, Oxley and Short, *J.*, 1946, 149; Part II, Oxley, Partridge, Robson, and Short, *ibid.*, p. 763; Part IV, Partridge and Short, *J.*, 1947, 390; Part VII, Oxley, Partridge, and Short, *ibid.*, p. 1110).

Trichloromethyl Cyanide and Ammonia.—Dry ammonia was passed for 2 hours at 0° into a solution of trichloromethyl cyanide (7 g.; b. p. 84—84·5°) in benzene (20 c.c.) and the solvent was then removed in a vacuum below 0°. The product was an oil and was therefore neutralised to bromocresol-purple with ethanolic picric acid, and concentration of the solution afforded slender yellow needles of *trichloroacetamidinium picrate*, which changed into stout needles at 220—223° and had m. p. 273—275° (decomp.) (Found: N, 17·8. $C_8H_6O_7N_5Cl_3$ requires N, 17·9%). Trichloroacetamidine was obtained as a solid, m. p. 41—42°, by the I.G. (*loc. cit.*) but was not analysed.

Trichloromethyl Cyanide and Aniline.—These reagents (1 mol. each) were recovered unchanged after a benzene solution of them had been kept at 20° for an hour.

Trichloromethyl Cyanide and Ethylenediamine.—A solution of trichloromethyl cyanide (5·78 g.) in dry benzene (10 c.c.) was added dropwise to a stirred solution of anhydrous ethylenediamine (1·2 g.; 1·0 mol.) in benzene (10 c.c.) at 0°. After the mixture had been stirred at 0° for 15 minutes and at 20° for 30 minutes, the solid (4·4 g.; 63%), m. p. 94—96°, was collected, and crystallised from benzene (15 c.c.) in rods, m. p. 97—98° (slight decomp.) (Found: N, 15·9. $C_6H_8N_4Cl_6$ requires N, 16·05%. $C_4H_8N_2Cl_2$ requires N, 14·9%). In agreement with the I.G. (*loc. cit.*), who give m. p. 88—90° but record no analysis, the compound is therefore NN-*ethylenebistrichloroacetamidine* and not 2-trichloromethyl-4 : 5-dihydroglyoxaline. The *bispicrate* crystallised from methanol in needles, m. p. 178° (decomp.) (Found: N, 17·4. $C_{18}H_{14}O_{14}N_{10}Cl_6$ requires N, 17·35%). The *bistoluene*-p-*sulphonate* separated from *iso*propanol in plates, m. p. 254° (decomp.) (Found: N, 7·9. $C_{20}H_{24}O_6N_4Cl_6S_2$ requires N, 8·1%), and from water in small plates, m. p. 210° (Found: N, 8·0%).

Phenyl Cyanide and Piperidine.—Phenyl cyanide (5·2 g.) and piperidine (4·25 g.; 1 mol.) were heated at 180° for 3 hours in a sealed tube, and the product was separated into a basic and a neutral fraction. Phenyl cyanide, b. p. 56°/5 mm. (4·6 g.; 88·5%), was recovered, and distillation of the basic fraction gave piperidine and a fraction, b. p. 114°/1 mm., which afforded *NN*-pentamethylenebenzamidinium picrate (0·32 g., 1·5%), m. p. and mixed m. p. 173—174° (Part IV).

3 : 6-*Dihydroxy*-o-*phenylene Dicyanide and Ammonia.**—The yellow needles prepared from the dicyanide and cold alcoholic ammonia, as described by Drew and Kelly (*loc. cit.*), blackened and decomposed between 200° and 280° without melting. An aqueous solution of this compound had a greenish-blue fluorescence, was alkaline to brilliant-yellow but not to Titan-yellow, afforded ammonia with cold aqueous sodium hydroxide, and did not respond to Fuller's amidine reagent (*Nature*, 1944, **154**, 773). When acetic acid (0·2 c.c.) was added to a solution of the yellow compound (147 mg.) in water and the white needles so obtained were dried in a vacuum at room temperature, they darkened at 230—250° without melting (Found: N, 17·25. Calc. for $C_8H_4O_2N_2$: N, 17·5%). Thiele and Meisenheimer (*Ber.*, 1900, **33**, 675) state that 3 : 6-dihydroxy-o-phenylene dicyanide darkens at *ca.* 230°. Acetylation of this regenerated dicyanide (53 mg.) with acetic anhydride (0·4 c.c.) in dry pyridine (0·8 c.c.) for 12 hours afforded 3 : 6-*diacetoxy*-o-*phenylene dicyanide*, m. p. 166—168° (Found: N, 11·7. $C_{12}H_8O_4N_2$ requires N, 11·5%), identical with a specimen prepared from authentic 3 : 6-dihydroxy-o-phenylene dicyanide. It is therefore clear that the yellow compound is the diammonium salt of 3 : 6-dihydroxy-o-phenylene dicyanide and not the corresponding diamidine.

p-*Methylsulphonylphenyl Cyanide and Ammonia.*—(*a*) *p*-Methylsulphonylphenyl cyanide (5 g.) was heated at 180° for 3 hours in an atmosphere of ammonia, and the product was cooled, suspended in water (5 c.c.), and neutralised to brilliant-yellow with hydrochloric acid. The solid was collected, washed with water (2 × 3 c.c.), and separated by acetone into a soluble portion consisting of *p*-methylsulphonylphenyl cyanide, m. p. 142° (4·52 g., 91%), and the almost insoluble 2 : 4 : 6-tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine (Found: N, 7·8. Calc. for $C_{24}H_{21}O_6N_3S_3$: N, 7·7%) (0·35 g. or 6·9%; Part VII). When sodium picrate was added to the amidinium chloride solution and washings, *p*-methylsulphonylbenzamidinium picrate, m. p. 261—262° (Part IV), was obtained (0·14 g., 1·2%).

(*b*) *p*-Methylsulphonylbenzamidine (4·94 g.) was heated at 180° for 3 hours in an atmosphere of ammonia, and the product afforded *p*-methylsulphonylphenyl cyanide, m. p. and mixed m. p. 142° (3·10 g., 68·7%), 2 : 4 : 6-tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine, m. p. > 360° (1·26 g., 27·9%), and *p*-methylsulphonylbenzamidinium picrate, m. p. 260° (0·11 g., 1·1%), or 262° after recrystallisation from ethanol. A small quantity of the cyanide, m. p. 139—140°, sublimed from the reaction mixture. In another experiment, the amidine (0·618 g.) was heated at 180° for 3 hours and the ammonia evolved was collected in 0·1N-hydrochloric acid, the residual gas being displaced by a stream of dry air. The ammonia evolved neutralised 30·45 ml. of 0·1N-acid and represented decomposition of 97·6% of the amidine. Unchanged amidine, the cyanide, and the triazine were identified in the residue.

(*c*) When the cyanide (1·8 g.) and urea (2·4 g.; 4 mols.) were stirred at 180° for 2 hours, the product on being worked up as described above afforded 0·08 g. (2%) of *p*-methylsulphonylbenzamidinium picrate, m. p. and mixed m. p. 262°.

* Experiments by Mr. F. F. Whitmont.

p-*Methylsulphonylphenyl Cyanide and Dimethylamine.*—A steady stream of dimethylamine was passed into the molten cyanide (4·5 g.) at 180° for 3 hours and the unchanged cyanide (4·4 g., 98%) and amidine were separated as described in the previous section. The yield of *NN*-dimethyl-*p*-methylsulphonylbenzamidinium picrate, m. p. and mixed m. p. 187—189° (Part IV), was 0·08 g. (0·7%).

p-*Methylsulphonylphenyl Cyanide and 2-Aminopyridine.*—A mixture of the cyanide (9·05 g.) and 2-aminopyridine (4·7 g.; 1 mol.) was kept at 180° for an hour and afforded unchanged cyanide (7·5 g.; 83%) and *N*-2-pyridyl-*p*-methylsulphonylbenzamidine (1·5 g., 11%), m. p. and mixed m. p. 169—170° (Part VII).

p-*Methylsulphonylphenyl Cyanide and Piperidine.*—The cyanide (9·05 g.) and amine (8·5 g.; 2 mols. were heated in a sealed tube for 18 hours at 175—180° and afforded 6·7 g.(74%) of recovered cyanide, m. p. 140—142°, and 3·1 g. (24%) of crude amidine, which gave 5·1 g. of pure *NN*-pentamethylene-*p*-methylsulphonylbenzamidinium picrate, m. p. and mixed m. p. 199—199·5° (Part VII).

p-*Methylsulphonylphenyl Cyanide and Aniline.*—The formation of amidine could not be detected, and the cyanide, m. p. 142°, was recovered quantitatively when *p*-methylsulphonylphenyl cyanide (4·5 g.) and aniline (9·3 g.; 4 mols.) were heated at 180° for 3 hours. *N*-Phenyl-*p*-methylsulphonylbenzamidine, m. p. 231° (Part IV), was recovered unchanged after heating at 180° for 3 hours.

2 : 4-*Dichlorophenyl Cyanide and Aniline.*—After 2 : 4-dichlorophenyl cyanide (Gomberg and Cone, *Annalen*, 1909, **370**, 182) (1·72 g.) and aniline (0·93 g.; 1 mol.) had been heated at 180° for 5 hours, 99% of the cyanide, m. p. and mixed m. p. 59—60°, was recovered and no amidine could be detected in the product. A mixture of the cyanide (3·44 g.) and anilinium benzenesulphonate (5·02 g.; 1 mol.) was heated at 190° for 4½ hours, and crystallisation of the product from water gave colourless prisms of N-*phenyl*-2 : 4-*dichlorobenzamidinium benzenesulphonate*, m. p. 183—183·5° (Found: N, 6·4, 6·5. $C_{19}H_{16}O_3N_2Cl_2S$ requires N, 6·6%). The *amidine* separated from light petroleum (b. p. 100—120°) in needles, m. p. 102° (Found: N, 10·6. $C_{13}H_{10}N_2Cl_2$ requires N, 10·6%), and afforded a *picrate*, m. p. 156·5° (Found: N, 13·9. $C_{19}H_{13}O_7N_5Cl_2$ requires N, 14·2%).

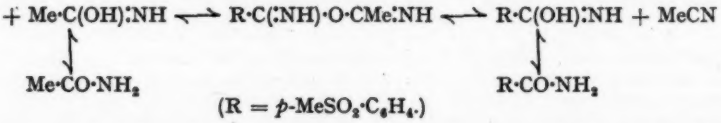
Preparation of Amidines from Cyanides, Ammonia or an Amine, and an Ammonium Salt.

p-*Methylsulphonylbenzamidine.*—(*a*) *p*-Methylsulphonylphenyl cyanide (9·05 g.) and ammonium benzenesulphonate (8·8 g.; 1 mol.) were heated at 180° for 2½ hours, a stream of dry ammonia being passed into the mixture, which solidified during the course of the reaction. The product was triturated with acetone to remove unchanged cyanide (1·45 g., 16%), and the insoluble portion was crystallised from hot water, giving 14·8 g. (83%) of *p*-methylsulphonylbenzamidinium benzenesulphonate, m. p. and mixed m. p. 253° (Part I). When the mixture was heated at 153° the yield of amidinium salt was 42 and 65% after 8·5 and 15½ hours, respectively. Addition of various "fluxes" to an equimolecular mixture of the cyanide and ammonium benzenesulphonate, so that the mixture remained homogeneous during the passage of ammonia, resulted in reduced yields in this instance, as shown in the table.

Flux.	Mols.	Temp.	Time, hrs.	Amidine, %.	Recovered cyanide, %.
Guanidinium benzenesulphonate	1·0	180°	5	79	—
N-Methylpyridinium benzenesulphonate	1·6	160	15·5	65	—
	1·6	160	4	51	31
Acetamide	3·4	180	2	39	58
Triethylammonium benzenesulphonate	0·8	160	2	Trace *	90

* The product gave a positive reaction with the Fuller reagent.

(*b*) (i) No amidine could be detected with Fuller's reagent in the mixture obtained by heating the cyanide and ammonium chloride (4 mols.) at 180° for 3½ hours. (ii) When dry ammonia was passed for 2½ hours into a mixture of the cyanide (9·05 g.) and ammonium chloride (2·7 g.; 1 mol.) at 180°, *p*-methylsulphonylbenzamidine, isolated as picrate (3·2 g.), m. p. and mixed m. p. 265°, was obtained in 15% yield, and 62% of the cyanide was recovered. (iii) A solid began to separate after *ca.* 2½ hours when ammonia was passed into the homogeneous solution obtained by heating the cyanide (4·5 g.), ammonium chloride (1·5 g.; 1·1 mols.), and acetamide at 180°. The operation was interrupted after 5 hours, the product was cooled and triturated with acetone, and the insoluble solid was collected by filtration. The filtrate was evaporated, and the residue crystallised from methanol, giving crude *p*-methylsulphonylphenyl cyanide (0·25 g.; 6%), m. p. 136—138°. The acetone-insoluble solid was stirred with cold water and an insoluble portion was removed by filtration. *p*-Methylsulphonylbenzamidinium toluene-*p*-sulphonate (4 g.; 43%), m. p. and mixed m. p. 293° (Part VII), separated when aqueous ammonium toluene-*p*-sulphonate was added to the filtrate. The solid insoluble in cold water was crystallised from hot water and afforded *p*-methylsulphonylbenzamide (2·1 g., 42%), m. p. and mixed m. p. 226—227° (Part II). Since all the substances used in this reaction were dry, it is probable that this amide is produced by an exchange of functions between acetamide and the cyanide, possibly by the mechanism:



(R = *p*-$MeSO_2·C_6H_4$.)

(*c*) *p*-Methylsulphonylphenyl cyanide (9 g.) and ammonium thiocyanate (3·8 g.; 1 mol.) were heated at 180° for 1½ hours in a stream of ammonia; the amidine was isolated and converted into *p*-methylsulphonylbenzamidinium chloride (8·6 g.; 74%), m. p. and mixed m. p. 295°. 2 : 4 : 6-Tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine (1 g.) was obtained from the neutral portion of the product.

p-Methylsulphonylbenzamidine (3·2 g.; 54%), m. p. and mixed m. p. 201—202° (decomp.), was isolated from the mixture obtained by heating the cyanide (5·4 g.), ammonium thiocyanate (2·3 g.; 1 mol.), and urea (9 g.; 5 mols.) at 180° for 1½ hours.

(*d*) Dry ammonia was passed for 2½ hours into a mixture of the cyanide (9·05 g.) and ammonium methanesulphonate (5·7 g.; 1 mol.) heated at 180°, and the unchanged cyanide (0·5 g.; 6%) was extracted from the product by trituration with acetone. The residue was dissolved in a solution of ammonium benzenesulphonate (20 g.) in hot water (50 c.c.), and the *p*-methylsulphonylbenzamidinium benzenesulphonate (14·2 g.; 81%) which separated on cooling had m. p. and mixed m. p. 253°.

(*e*) *Ammonium* p-*hydroxybenzenesulphonate*, prepared from its constitutents, separated from water in colourless plates, m. p. 270—271° (decomp.) (Found: N, 7·4. $C_6H_9O_4NS$ requires N, 7·3%). When the cyanide (5·43 g.) and this salt (5·73 g.; 1 mol.) were heated at 195° for 1½ hours in an atmosphere of ammonia, the product contained unchanged cyanide (4·4 g.; 81%), m. p. 140—141°, and the amidine, which was isolated as toluene-*p*-sulphonate (2 g.; 18·3%), m. p. and mixed m. p. 293—294° (Part VII).

NN-*Dimethyl*-p-*methylsulphonylbenzamidine*.—In the following experiments the reaction product contained unchanged *p*-methylsulphonylphenyl cyanide, 2 : 4 : 6-tris-*p*-methylsulphonylphenyl-1 : 3 : 5-triazine, *p*-methylsulphonylbenzamidinium benzenesulphonate, and its *NN*-dimethyl derivative. The amidines were separated by taking advantage of the distinct solubility of the substituted amidine in aqueous alkali (cf. Part IV). The unsubstituted amidine was extracted from the insoluble portion with dilute hydrochloric acid, and the residual cyanide and triazine were separated by extracting the cyanide with acetone.

(*a*) *p*-Methylsulphonylphenyl cyanide (9 g.) and ammonium benzenesulphonate (8·75 g.; 1 mol.) were heated at 180° and stirred for 3 hours, a slow stream of dry dimethylamine being passed into the mixture. A homogeneous melt was produced after 20 minutes, persisted for *ca.* 40 minutes, and then became increasingly turbid. When a hot solution of the product in water (40 c.c.) was poured into a mixture of 10N-sodium hydroxide (20 c.c.) and ice (20 g.), dimethylamine was evolved, and the solid which separated was collected after an hour and washed with a little ice-water, and the united filtrates were kept. The solid (3·04 g.) was suspended in water, acidified to Congo-red with dilute hydrochloric acid (2 drops), and the whole filtered. The solution gave no colouration with Fuller's reagent and afforded no precipitate with aqueous sodium picrate. The solid was separated by acetone into unchanged cyanide, m. p. and mixed m. p. 141—142° (1·96 g.; 21·8%), and the triazine (1·07 g.; 11·9%). The original filtrate was extracted with chloroform (6 × 100 c.c.), the solution dried (K_2CO_3) and evaporated, and the residual gum (5·9 g.) dissolved in water (25 c.c.), neutralised to brilliant-yellow with dilute hydrochloric acid, and diluted to 50 ml. The *NN*-disubstituted amidine gave no colouration with Fuller's reagent, and the *p*-methylsulphonylbenzamidinium chloride in 1 ml. of the solution was determined colorimetrically (Fuller, *Biochem. J.*, 1945, **39**, 99) and found to be equivalent to 3·3 mg. in the whole solution. The remaining solution (49 ml.) was evaporated on the steam-bath and the residue, dried at 100°, was equivalent to 6·87 g. of the *NN*-dimethylbenzamidinium chloride in 50 ml. of solution. The amidinium chloride was purified with considerable loss by dissolving it in the minimum quantity of 1 : 1 aqueous acetone (charcoal) and pouring the filtered solution into a large excess of acetone, and was obtained in colourless plates, m. p. 274—275° (decomp.), undepressed on admixture with an authentic specimen.

(*b*) A stream of dry ammonia was passed for 3 hours into a mechanically stirred mixture of *p*-methylsulphonylphenyl cyanide (9 g.) and dimethylammonium benzenesulphonate (11·5 g.; 1 mol.) kept at 180° in the vapour of phenol. The clear melt became increasingly turbid during the last two hours' heating. A hot solution of the product in water (40 c.c.) was poured into 10N-sodium hydroxide (20 c.c.) and ice (20 g.), and the solid (A) was collected after 2½ hours and washed with water (3 × 5 c.c.) and chloroform (3 × 5 c.c.). The aqueous filtrate was extracted with chloroform (6 × 50 c.c.), and the united chloroform solutions were dried (K_2CO_3) and evaporated, giving a pale yellow gum (3·4 g.). A small amount of a flocculent solid remained undissolved when this gum was added to water (5 c.c.), and was collected, washed with water (5 c.c.), and added to the solid (A). The filtrate, which gave a faint colouration with Fuller's reagent, was neutralised to brilliant-yellow with alcoholic picric acid, cooled to 0°, and filtered. The *NN*-dimethyl-*p*-methylsulphonylbenzamidinium picrate so obtained (2·95 g.) had m. p. 185—186°, alone or on admixture with an authentic specimen, m. p. 189·5° (Part IV). The solid (A) was suspended in water (10 c.c.), and dilute hydrochloric acid was added until the solution was neutral to brilliant-yellow. The insoluble solid (B) was then removed, the filtrate was poured into 10N-sodium hydroxide (5 c.c.) and ice (10 g.), and filtered after an hour. The solid was washed with water, suspended in water (20 c.c.), and neutralised to Congo-red with aqueous benzenesulphonic acid. The resulting solution was warmed with charcoal, filtered, and evaporated to dryness under diminished pressure. The residual *p*-methylsulphonylbenzamidinium benzenesulponate (8·5 g.) had m. p. 250—251°, undepressed on admixture with an authentic specimen (Part I). The solid (B) was separated by acetone into *p*-methylsulphonylphenyl cyanide, m. p. and mixed m. p. 138—140° (1 g.; 11·1%), and the triazine (0·93 g.; 10·3%).

(*c*) In this experiment the cyanide (6·8 g.) and dimethylammonium benzenesulphonate (8·66 g.; 1 mol.) were heated and stirred at 180° for 3 hours, and dry ammonia (900 c.c. at 19° and 762 mm.; 1 mol.) was passed to and fro over the reaction mixture. At the end of 3 hours the volume of the residual gas was 657 c.c. (19°/762 mm.). Recovered cyanide (1·2 g.), triazine (0·5 g.), *p*-methylsulphonylbenzamidinium benzenesulphonate (3·2 g.), and *NN*-dimethyl-*p*-methylsulphonylbenzamidinium picrate (6·4 g.) were isolated and identified as described in (*b*).

(*d*) When the cyanide (4·5 g.) and dimethylammonium benzenesulphonate (5·8 g.; 1 mol.) were heated at 180° for 3 hours and the cold mixture was extracted with acetone, dimethylammonium benzenesulphonate, m. p. 110° (5·3 g.; 92%), remained and the solution afforded unchanged cyanide (4·36 g.; 97%). No picrate could be obtained from the mother-liquor, indicating that there is no appreciable formation of amidine at 180°. This is in accord with the observation (Part VII) that the cyanide and diethylammonium benzenesulphonate give only 7% of the corresponding *NN*-diethylamidine at 224°.

NN′-*Dibenzyl*-p-*methylsulphonylbenzamidine*.—*p*-Methylsulphonylphenyl cyanide (9 g.), ammonium benzenesulphonate (8·8 g.; 1 mol.), and benzylamine (10·7 g.; 2 mols.) were heated at 180° for 2 hours, and the cold product was stirred with dilute hydrochloric acid. The oil which separated was dissolved in chloroform, and the solution was washed with a little water to remove benzylammonium chloride, shaken with aqueous sodium hydroxide to decompose the hydrochlorides, and then evaporated. The residue was dissolved in dilute hydrochloric acid and ammonia was added to the solution to precipitate NN′-*dibenzyl*-p-*methylsulphonylbenzamidine*, which crystallised from methanol in needles, m. p. 129—131° (Found: N, 7·4. $C_{22}H_{22}O_2N_2S$ requires N, 7·4%); yield, 1·2 g. (6·35%).

p-*Nitrobenzamidine*.—(*a*) *p*-Nitrophenyl cyanide (4·95 g.) and ammonium benzenesulphonate (5·85 g.; 1 mol.) were heated at 180° for 2 hours, during which a stream of dry ammonia was passed into the mixture. Acetone extracted unchanged cyanide (35%) from the product, and crystallisation of the insoluble fraction from water afforded *p*-nitrobenzamidinium benzenesulphonate (52%), m. p. and mixed m. p. 258—259° (Part I). Rouiller (*Amer. Chem. J.*, 1912, **47**, 483) records m. p. 250°.

(*b*) *p*-Nitrophenyl cyanide (1·5 g.), benzenesulphonic acid monohydrate (1·9 g.; 1·1 mol.), and urea (2·4 g.; 4 mols.), heated at 180° for 1½ hours so that water vapour and ammonia were allowed to escape, afforded a 27% yield of *p*-nitrobenzamidinium benzenesulphonate, m. p. and mixed m. p. 258°, and 54% of the cyanide was recovered.

3 : 5-*Dinitrobenzamidine*.—A stream of dry ammonia was passed into a molten mixture of 3 : 5-dinitrophenyl cyanide (3·86 g.) and ammonium benzenesulphonate (3·5 g.; 1 mol.) which was kept at 195°. After 15 minutes' heating the mixture had solidified and was then cooled, triturated with acetone, and filtered. The solid was crystallised from water and gave 3 : 5-*dinitrobenzamidinium benzenesulphonate*, m. p. 265° (Found: N, 15·3. $C_{13}H_{12}O_7N_4S$ requires N, 15·2%); yield, 61%. 3 : 5-*Dinitrobenzamidinium picrate* had m. p. 271° (Found: N, 22·4. $C_{13}H_9O_{11}N_7$ requires N, 22·3%).

2 : 4-*Dinitrobenzamidine*, 2 : 4-*Dichlorobenzamidine*, *and* 2 : 6-*Dimethoxybenzamidine*.—When the corresponding cyanides and ammonium benzenesulphonate (1 mol.) were heated at 180° for 3 hours in an atmosphere of ammonia, the products all gave colourations with Fuller's reagent, but the amount of amidines produced was small and they were not isolated.

4 : 4′-*Diamidino*-αγ-*diphenoxypropane*.—Dry ammonia was passed for 24 hours into a mechanically stirred mixture of 4 : 4′-dicyano-αγ-diphenoxypropane (28 g.) and ammonium benzenesulphonate (35 g.; 2 mols.) heated in a bath at 210—212°. The amidinium chloride, isolated in the usual way (Part IV), had m. p. and mixed m. p. 294° (18·8 g., 48%).

4 : 4′-*Diamidinostilbene*.*—4 : 4′-Dicyanostilbene (46 g.) and ammonium benzenesulphonate (70 g.; 2 mols.) were heated at 270—275° and a stream of ammonia was passed into the melt for 3 hours with vigorous stirring. The amidinium sulphonate was separated from unchanged cyanide (14 g.; 30%) by solution in boiling water, and the amidine was liberated with 5N-sodium hydroxide and converted into 4 : 4′-diamidinostilbene dihydrochloride dihydrate, m. p. 372—375° (decomp.) (Found: N, 14·9; Cl, 18·8. Calc. for $C_{16}H_{18}N_4Cl_2,2H_2O$: N, 15·0; Cl, 19·0%). The m. p. depends upon the rate of heating (cf. Part IV); yield, 45·5 g. (61%).

2-*Amidinopyridine*.—2-Cyanopyridine (4·2 g.), ammonium benzenesulphonate (7 g.; 1 mol.), and urea (9·6 g.; 4 mols.) were heated at 180° and stirred for 2 hours. The mixture was cooled, triturated with water (50 c.c.), and then extracted with chloroform (3 × 10 c.c.). The aqueous solution was made alkaline with 10N-sodium hydroxide at 0° and the amidine was extracted with chloroform (7 × 20 c.c.). The chloroform solution was dried (Na_2SO_4) and evaporated, and saturated alcoholic picric acid was added to the residue until the mixture was neutral to brilliant-yellow; it was then cooled to 0° and filtered, giving 3·4 g. (24%) of the picrate of 2-amidinopyridine, m. p. 202—203°. Recrystallisation from methanol raised the m. p. to 207—208°, not depressed on admixture with an authentic specimen (Part I).

Phenylacetamidine.—Benzyl cyanide (11·7 g.) and ammonium benzenesulphonate (3·5 g.; 0·2 mol.) were heated at 195° for 8 hours, during which a steady stream of ammonia was passed into the mixture. The cooled product was diluted with acetone and filtered, and the solid was washed with acetone and crystallised from water, giving phenylacetamidinium benzenesulphonate, m. p. and mixed m. p. 186° (Part IV); yield, 15%.

N-cyclo*Hexylphenylacetamidine*.—(*a*) The product obtained by heating benzyl cyanide (11·7 g.), *cyclo*hexylamine (19·8 g.; 2 mols.), and ammonium chloride (5·4 g.; 1 mol.) at 180° for 8 hours was triturated with water (20 c.c.) and the mixture was made acid to Congo-red with 5N-hydrochloric acid. The solid was collected, washed with benzene, and crystallised from alcohol, giving 18·9 g. (75%) of *N-cyclo*hexylphenylacetamidinium chloride, m. p. 290—292° (decomp.). A second recrystallisation from alcohol afforded the pure compound, m. p. and mixed m. p. 303—304° (decomp.) (Part VII).

(*b*) An 84% yield of the amidinium chloride, m. p. and mixed m. p. 302—303° (decomp.), was obtained by heating benzyl cyanide (11·7 g.), *cyclo*hexylamine (9·9 g.; 1 mol.), and *cyclo*hexylammonium chloride (13·5 g.; 1 mol.) at 180° for 8 hours.

(*c*) Benzyl cyanide (11·7 g.), *cyclo*hexylamine (19·8 g.; 2 mols.), and pyridinium benzenesulphonate (23·7 g.; 1 mol.) were heated under reflux at 180° for 4 hours, and the bases were then liberated with ice-cold 2·5N-sodium hydroxide and collected in chloroform. The chloroform solution was washed with 2·5N-sodium hydroxide (2 × 20 c.c.) and water (5 c.c.), dried (K_2CO_3), and evaporated. Pyridine was removed by distilling the mixture of bases at 2 mm. until the temperature reached 82°, and the residue was then warmed with 3·3N-hydrochloric acid (15 c.c.). The solution was cooled, and the solid was collected and washed with benzene, giving 2·2 g. (8·8%) of *N-cyclo*hexylphenylacetamidinium chloride, m. p. 290—292° (decomp.).

N-cyclo*Hexyl*-1-*amidino*-n-*heptane*.—*n*-Heptyl cyanide (2·5 g.), *cyclo*hexylamine (1 g.; 0·5 mol.), and *cyclo*hexylammonium toluene-*p*-sulphonate (5·4 g.; 1 mol.) were heated at 190—195° for 5 hours under a reflux condenser. The product was dissolved in chloroform, and after the solution had been washed several times with 2N-sodium hydroxide, chloroform was removed by distillation.

* Experiment by Mr. S. W. Stroud.

2N-Hydrochloric acid was added to the residue until the mixture was acid to Congo-red, and the solid was then collected and crystallised from water, giving the hydrochloride of *N-cyclo*hexyl-1-amidino-*n*-heptane, m. p. and mixed m. p. 200° (Part VII); yield, 0·63 g. (12%).

RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO. LTD., NOTTINGHAM.

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77. *Esters of 1-Hydroxy-2-naphthoic Acid, and Naphthol-blue Dyes therefrom.*

By M. PIANKA and H. C. BARANY.

The preparation of esters of 1-hydroxy-2-naphthoic acid and naphthol-blue dyes derived from them is discussed. The stability of these dyes is compared with those derived from esters of salicylic acid.

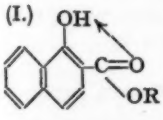
1-HYDROXY-2-NAPHTHOIC acid was prepared by passing dry carbon dioxide for 14 hours over powdered anhydrous sodium α-naphthoxide placed in a uniformly heated tube at a constant temperature which lay between 80° and 140° according to requirements (cf. Lassar-Cohn and Loewenstein, *Ber.*, 1908, **41**, 3365). By reaction of the acid chloride with the corresponding

Physical properties of the dyes $O{:}C_{10}H_5(CO_2R){:}N{\cdot}C_6H_4{\cdot}NEt_2$.

R.	Colour of dye crystals.	M. p.	Recryst. from :	Abs. max. (A.) in $COMe_2$.	Found, %. C.	H.	N.	Formula.	Required, %. C.	H.	N.
Me	Dark blue	157—158°	Dil. MeOH	6200	72·9	6·1	7·9	$C_{23}H_{22}O_2N_2$	72·9	6·1	7·7
Et	Orange	141—142	PhMe–light pet.	6260	73·6	6·4	7·3	$C_{24}H_{24}O_2N_2$	73·4	6·4	7·4
Pr	Dark brown	149—150	,,	6310	73·9	6·6	7·3	$C_{25}H_{26}O_2N_2$	73·8	6·7	7·2
Bu	Dark blue	79—80	MeOH	6340	74·2	7·1	7·1	$C_{26}H_{28}O_2N_2$	74·2	6·9	6·9
Ph	Black	109—110	Dil. EtOH	6300	76·5	5·6	6·7	$C_{27}H_{24}O_2N_2$	76·4	5·7	6·6
CH_2Ph	Dark blue-green	67—68	,,	6430	76·6	6·0	6·3	$C_{28}H_{26}O_2N_2$	76·7	5·9	6·4

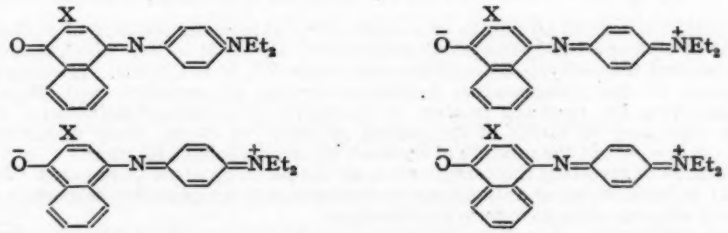
alcohol or its sodium derivative the esters were obtained. These were but sparingly soluble in alkali probably owing to chelation as in (I).

Derivatives of α-naphthol-blue were obtained from a dilute alcoholic solution of an ester and diethyl-*p*-phenylenediamine in alkaline medium by oxidising it with either (*a*) potassium persulphate or (*b*) silver halide by the action of light.

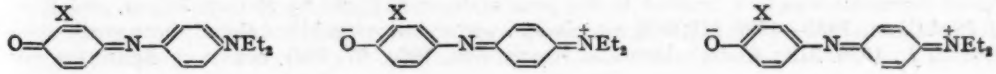
(I.) 

Only method (*a*) could be used for preparing the dyes of esters of salicylic acid, but these could not be isolated because of their instability (cf. Vittum and Brown, *J. Amer. Chem. Soc.*, 1946, **68**, 2236). The greater stability of the dyes obtained from the esters of 1-hydroxy-2-naphthoic acid could be explained by their ability to exhibit more resonance, thereby facilitating the dispersion of the negative charge of the polarised phenolic oxygen.

The possible resonance forms for the naphthol-blue *dyes* are (X = H or CO_2R) :



whereas those for phenol blue dyes are :



EXPERIMENTAL.

(M. p.s are uncorrected.)

1-Hydroxy-2-naphthoyl Chloride.—10 G. of the acid were refluxed with 12 c.c. of thionyl chloride in 50 c.c. of light petroleum (b. p. 60—80°) until an orange solution resulted. On evaporation under reduced pressure, yellow needles were obtained, m. p. 84°.

Esterification. The acid chloride was refluxed for 2 hrs. with 4 times its weight of the appropriate alcohol. On cooling in a freezing mixture, the ester crystallised. If crystallisation did not set in, the alcohol was distilled off on the water-bath, and the residual oil under reduced pressure. The following 1-hydroxy-2-naphthoates were prepared : methyl, buff needles from alcohol, m. p. 76° (Schmidt and Burkhardt, *Ber.*, 1887, **20**, 2700; Cohen and Dudley, *J.*, 1910, **97**, 1747; Kaufmann and Egner, *Ber.*, 1913, **46**, 3782); ethyl, fine pale pink needles from alcohol, m. p. 46° (Schmidt and Burkhardt, *loc. cit.*; Lassar-Cohn and Loewenstein, *loc. cit.*); *propyl*, buff needles from alcohol, m. p. 63° (Found : C, 73·0; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%); iso*propyl*, buff platelets from alcohol, m. p. 51° (Found : C, 73·0; H, 6·1%); *butyl*, yellowish needles from alcohol, m. p. 40° (Found : C, 73·8; H, 6·5. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%); iso*butyl*, oil which distilled at 208°/45 mm. and solidified to a mass of yellowish needles from alcohol, m. p. 62° (Found : C, 73·8; H, 6·5%); *benzyl*, long white needles from alcohol, m. p. 72° (Found : C, 77·7; H, 5·0. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·0%).

Hexyl ester. This ester could not be obtained by the previous method, so the following procedure was adopted. To 8·8 g. of 1-hydroxy-2-naphthoyl chloride was added a cold solution of sodium hexyloxide in benzene, prepared by refluxing a mixture of 9·5 c.c. of *n*-hexyl alcohol and 1 g. of finely divided sodium in 200 c.c. of dry benzene for 10 hr.; the mixture was refluxed for 2 hr., the benzene distilled off, and the residual oil poured into crushed ice with stirring. The yellow precipitate so obtained was collected, and recrystallised from alcohol; white short needles, m. p. 43° (Found : C, 75·0; H, 7·4. $C_{17}H_{20}O_3$ requires C, 75·0; H, 7·3%).

Phenyl ester. A modification of Jusa and von Janovitch's method (*Monatsh.*, 1938, **71**, 205) was adopted. 3·78 G. of the acid and 0·55 c.c. of phosphorus oxychloride were added in three separate and equal portions to 1·88 g. of phenol at intervals of 30 mins. at a temperature of 110°. The mixture was maintained at this temperature until no more hydrogen chloride was evolved. To the cold mixture a little water was added. The resulting hard mass was broken up, washed until neutral, and then made alkaline (litmus) by addition of sodium carbonate solution. The precipitate was filtered off, washed till neutral, dried at 50°, stirred with methanol at 30°, and dried at 50°; m. p. 91°.

Naphthol-blue Dyes.—(a) *By oxidation with potassium persulphate.* 1 G. of the ester was dissolved in a small amount of ethanol to which was added 1 g. of diethyl-*p*-phenylenediamine hydrochloride. To the warm solution were added 2·5 g. of potassium persulphate and a few drops of 3N-sodium hydroxide. The blue-green dye was precipitated by water; in some cases it solidified only on cooling in a freezing mixture. The dye was filtered off, washed well with water, dried, and recrystallised.

(b) *By oxidation with silver halide exposed to light.* 0·5 G. of the ester, dissolved in 10 c.c. of ethanol, was added to 20 c.c. of a silver halide emulsion containing 10% of gelatin and 1·5% of calsolene oil (I.C.I.) in the dark. This emulsion was coated on a glass plate, dried, exposed to light for a few seconds, and developed in an alkaline solution of diethyl-*p*-phenylenediamine hydrochloride. The silver and silver halide were then removed, leaving a blue-green image.

Spectrophotometric Measurements.—All these were carried out on a Hilger spectrophotometer.

We are indebted to Mr. B. M. Ratner for making the spectrophotometric measurements, and to Mr. J. A. Parsons for the photographic tests.

Mr. Edgerton and the Directors of Dufay–Chromex Limited are thanked for permission to publish this work, and Mr. B. Gluck for suggesting the use of these compounds in colour photography.

RESEARCH LABORATORIES, DUFAY–CHROMEX LIMITED,
ELSTREE, HERTS.

[*Received, April 22nd*, 1947.]

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78. *A New Synthesis of* DL-*Threonine.*

By J. ATTENBURROW, D. F. ELLIOTT, and G. F. PENNY.

Condensation of sodium hippurate with acetic anhydride in the presence of β-picoline gave a high yield of 2-*phenyl*-4-(α-*hydroxyethylidene*)*oxazol*-5-*one* (I, R = Me), which was converted by boiling alcohol into ethyl α-benzamidoacetoacetate (II, R = CO_2Et). Hydrogenation of this compound to the corresponding hydroxy-ester was accomplished with Raney nickel catalyst, and from the resulting mixture of racemates DL-N-*benzoyl*allo*threonine ethyl ester* (VIII) was separated by virtue of its sparing solubility in ether. Pure DL-threonine was obtained from the part of the mixture of racemates that was soluble in ether.

Two methods of inverting the configuration at the β-carbon atom in the ester (VIII) have been found; in both instances a simultaneous ring closure to an oxazoline derivative occurred Hydrolysis of this oxazoline gave pure DL-threonine.

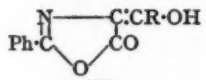
The total overall yield of DL-threonine from hippuric acid was about 30%, the greatest loss being incurred during the separation of the hydroxy-ester.

WHEN threonine was first isolated in the pure state from fibrin by McCoy, Meyer, and Rose (*J. Biol. Chem.*, 1935—1936, **112**, 283), α-amino-β-hydroxybutyric acid had already been synthesised (Burch, *J.*, 1930, 310; Abderhalden and Heyns, *Ber.*, 1934, **67**, 530), but its configuration was

unknown. A thorough investigation of the problem by Carter and his collaborators (*J. Biol. Chem.*, 1935—1936, **112**, 769; 1937, **117**, 1; 1937, **119**, 103, 109) culminated in a satisfactory laboratory-scale synthesis of pure DL-threonine from crotonic acid (Carter and West, *Org. Synth.*, 1940, **20**, 101). A simpler synthesis has been described by Adkins and Reeve (*J. Amer. Chem. Soc.*, 1938, **60**, 1328), but the purity of the product was not confirmed.

In connection with work relating to the synthesis of penicillin it seemed of interest to examine the action of acetic anhydride on sodium hippurate. It was found that when the substances were heated together for a few minutes at 100° there was produced in about 15% yield an unstable substance, $C_{11}H_9O_3N$, which was decomposed rapidly on continued heating of the reactants. Investigations on the structure of this compound were anticipated by workers at Oxford University, their results being made known to us in the form of a report to the Committee for Penicillin Synthesis (H. R. Bentley and Lady G. M. Robinson, C.P.S. 441, March 20th, 1945). In this report compounds prepared analogously from cinnamoylglycine were shown to be of the type (I), but with ·CH:CHPh instead of Ph. We found that the compound $C_{11}H_9O_3N$ was also a member of this group and it was therefore formulated as *2-phenyl-4-(1-hydroxyethylidene)oxazol-5-one* (I, R = Me). Details of our investigations were described in a report from these laboratories (C.P.S. 490, May 1st, 1945). The work now described formed a separate programme of research, but publication has been delayed because the initial experiments were carried out under a penicillin project.

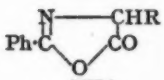
On boiling with water the oxazolone (I, R = Me) rapidly dissolved with evolution of carbon dioxide and yielded benzamidoacetone (II, R = H), whereas with boiling alcohol a quantitative yield of ethyl α-benzamidoacetoacetate (II, R = CO_2Et) was obtained. On being heated under reduced pressure this β-keto-ester was partly reconverted into the oxazolone; although various conditions were tried, the conversion could never be made complete.



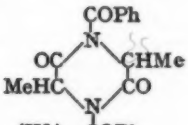
(I.)

$CH_3{\cdot}CO{\cdot}CHR{\cdot}NH{\cdot}COPh$

(II.)



(III.)



(IV.)

An attempt to prepare 4-acetyl-2-phenyl-4-methyloxazol-5-one by reaction of the sodium salt of benzoyl-α-alanine with acetic anhydride was not successful, the products consisting of *methyl 1-benzamidoethyl ketone* (II, R = Me), 2-phenyl-4-methyloxazol-5-one (III, R = Me), and a *compound*, $C_{18}H_{18}O_4N_2$, which may have been the diketopiperazine (IV).

The formation of an acylamido-ketone from benzoyl-α-alanine under base-catalysed conditions was not unexpected, in view of the work of Dakin and West (*J. Biol. Chem.*, 1928, **78**, 91, 745), who showed that hippuric acid, glycine, and many other amino-acids were converted into α-acetamido-ketones, with evolution of carbon dioxide, when heated with acetic anhydride and pyridine for several hours. Except for glycine and hippuric acid the reaction proceeded smoothly and the yields were good: $R{\cdot}CH(NH_2){\cdot}CO_2H \longrightarrow R{\cdot}CH(NHAc){\cdot}CO{\cdot}CH_3$. The oxazolone (I, R = Me) was also formed in the presence of a base under far less vigorous conditions, and it seemed possible, therefore, that oxazolones of type (I) were precursors of the acetamido-ketones prepared by Dakin and West and that the use of pyridine as a catalyst under mild conditions would lead to improved yields of the required oxazolone. Accordingly the effect of pyridine as a catalyst in the reaction between hippuric acid and acetic anhydride at room temperature was studied. It was found that the oxazolone (I, R = Me) was produced quite rapidly under these conditions, but simultaneous decomposition precluded good yields. An attempt to test the hypothesis that oxazolones exemplified by (I) were precursors of the acetamido-ketones described by Dakin and West (*loc. cit.*) gave inconclusive results. The oxazolone (I, R = Me) decomposed rapidly when heated with a mixture of acetic anhydride, pyridine, and some acetic acid, but only 50% of the theoretical amount of carbon dioxide was evolved and the ketonic product could not be obtained pure.

It was later found that the simultaneous decomposition of the oxazolone under the reaction conditions described was completely prevented by including one equivalent of sodium acetate in the reactants, or preferably by using sodium hippurate instead of hippuric acid. The catalytic properties of other bases in the pyridine series were also examined and some marked differences in activity were observed. It is noteworthy that dimethylaniline was found to be ineffective as a catalyst for the reaction under discussion, as it was for acetamido-ketone formation (Dakin and West, *loc. cit.*). β-Picoline was the most satisfactory catalyst, giving the highest yield and a clean product. The oxazolone was readily prepared on a substantial scale.

It is considered that the oxazolone (I, R = Me) is formed by a Claisen type of condensation between acetic anhydride and 2-phenyloxazol-5-one (III, R = H), which is in turn formed from hippuric acid or its sodium salt by the action of acetic anhydride. The high reactivity of the methylene group in 2-phenyloxazol-5-one under the catalytic influence of a tertiary base of the pyridine series was demonstrated by the reaction with acetic anhydride in the presence of pyridine to give a yield of the oxazolone (I, R = Me) higher than that obtained from sodium hippurate under the same conditions, by the reaction with propionyl chloride in the presence of β-picoline to give the homologous *2-phenyl-4-(1-hydroxypropylidene)oxazol-5-one* (I, R = Et), and by the strongly exothermic reaction with benzaldehyde to give 2-phenyl-4-benzylideneoxazol-5-one. The compound (I, R = Et) was also prepared in good yield from sodium hippurate and propionic anhydride in the presence of β-picoline.

The most significant experiments with hippuric acid, sodium hippurate, and 2-phenyloxazol-5-one are summarised in the table and were carried out at room temperature, the use of heat giving less satisfactory results owing to the instability of the product. It will be seen that sodium hippurate gave a higher yield than an equimolecular mixture of sodium acetate and hippuric acid (compare Expts. 3, 4, and 5 with Expt. 6). This indicates that acetic acid has an inhibitory effect on this reaction, because the formation of 2-phenyloxazol-5-one from one molecule of hippuric acid would liberate two molecules of acetic acid, whereas formation of the oxazolone from one molecule of sodium hippurate would liberate one molecule of acetic acid and one of sodium acetate whatever course this particular step in the reaction may take.

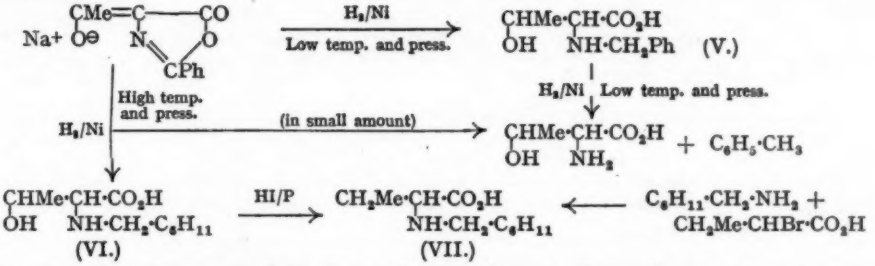
	Starting material and weight (g.).		Tertiary base, mols.		Ac_2O, mols.	NaOAc, mols.	Time, hrs.	Yield of (I), %.
1.	Hippuric acid,	7·2	Pyridine,	2	3	0	9	27·7
2.	,, ,,	7·2	,,	2	3	0	36	0
3.	,, ,,	17·9	,,	3	3	1	3	36·5
4.	,, ,,	17·9	,,	4	3	1	3	41·5
5.	,, ,,	17·9	,,	4	3	1	6	48
6.	Sodium hippurate,	20	,,	3	3	0	3	57·5
7.	2-Phenyloxazolone,	16·1	,,	2	2	1	3	76
8.	,, ,,	16·1	,,	2	2	0	1	34
9.	,, ,,	16·1	,,	2	2	1	1	48
10.	Sodium hippurate,	20	α-Picoline,	3	3	0	24	72 *
11.	,, ,,	20	β- ,,	3	3	0	3½	88
12.	,, ,,	20	γ- ,,	3	3	0	3½	87
13.	,, ,,	20	2 : 6-Lutidine,	3	3	0	24	18
14.	,, ,,	20	2 : 4 : 6-Collidine,	3	3	0	3½	73

* No signs of reaction after 6 hours.

Hydrogenation of the sodium salt of the oxazolone (I, R = Me) in aqueous solution could not be achieved with a platinum (Adams) catalyst or with small amounts of Raney nickel catalyst; in the presence of a large amount of the latter catalyst, 4 mols. of hydrogen were absorbed at a moderate rate and the products were α-amino-β-hydroxybutyric acid in 55% yield and toluene. When the hydrogenation was interrupted after absorption of 1 mol. of hydrogen a considerable amount of starting material was recovered and DL-N-*benzylallothreonine* (V) was isolated in 63% yield (based on oxazolone used). The structure of this compound follows from the fact that the amino-acid absorbed 1 mol. of hydrogen on further hydrogenation and yielded almost pure DL-*allo*threonine, shown by microbiological assay to possess only 1·5% of the activity of pure DL-threonine. It is possible that one of the first steps in the hydrogenation is addition of hydrogen to the ·C:N· link in the oxazolone ring, followed by ring opening and further addition of hydrogen. A detailed mechanism cannot be proposed on the basis of these preliminary experiments.

In an effort to devise more practicable hydrogenation conditions, the effect of using lese catalyst at high temperature and pressure was examined. Hydrogenation was much mors rapid, as would be expected, but under these conditions the main product was an amino-acid, $C_{11}H_{21}O_3N$, shown to be DL-α-cyclo*hexylmethylamino-β-hydroxybutyric acid* (VI). This was probably a mixture of stereoisomers, and to avoid difficulties in identification the asymmetry round the β-carbon atom was destroyed by reduction of the hydroxyl group with hydriodic acid and red phosphorus. The product, DL-α-cyclo*hexylmethylaminobutyric acid* (VII), formed in 60% yield, was converted into the *hydrochloride* and *ethyl ester hydrochloride*. *cyclo*Hexylmethylamine, prepared in good yield from cyano*cyclo*hexene by hydrogenation in alcoholic ammonia solution, was treated with α-bromobutyric acid in aqueous solution to give an authentic sample of α-*cyclo*hexylmethylaminobutyric acid for comparison.

This route did not give much promise of a useful synthesis of threonine and these experiments were discontinued.



Attention was then turned to the hydrogenation of ethyl α-benzamidoacetoacetate (II, R = CO_2Et). In alcoholic solution, with Raney nickel catalyst at elevated temperature and pressure, reduction took place readily. The resulting crude hydroxy-ester was hydrolysed directly with hydrobromic acid to give α-amino-β-hydroxybutyric acid in 64% yield from hippuric acid. When working on a large scale it was necessary to use impure materials and then it was frequently found that the oxazolone contained a detectable amount of an unknown sulphur compound; this must have been derived from the coal-tar base used as catalyst in the condensation. Fortunately the sulphur was readily removed by refluxing the alcoholic solution of the keto-ester with a small quantity of Raney nickel and filtering it before hydrogenation. Samples of amino-acid prepared in this way were found to contain 25—30% of DL-threonine and there was no significant change in the proportion of the required isomer when hydrogenations were carried out at various temperatures ranging from 80° to 160°.

Adkins and Reeve (*loc. cit.*) described a method of separating the amino-acids by a simple fractional crystallisation from water, and, although admitting that purity could only be checked by microbiological assay, they offered no proof that pure DL-threonine was obtained in this way: we were unable to obtain it pure by their method. Carter and West (*J. Biol. Chem.*, 1937, **117**, 1; **119**, 109) also report that fractional crystallisation of the amino-acids was impracticable.

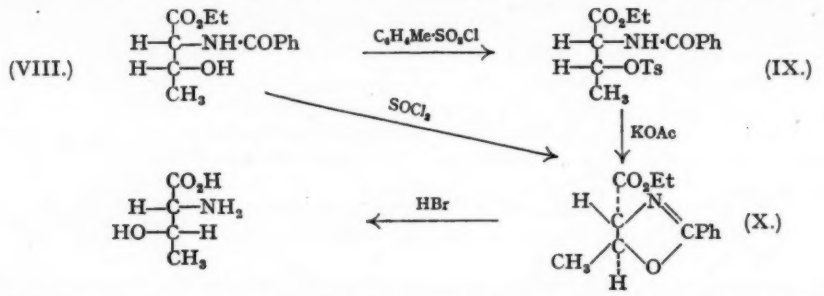
We found that the crude ethyl α-benzamido-β-hydroxybutyrate could be satisfactorily resolved into a solid and an oily ester with the aid of ether. The former was proved to be DL-N-*benzoyl*allo*threonine ethyl ester* (VIII), because it yielded on acid hydrolysis an amino-acid possessing no growth-promoting properties, and, on mild alkaline hydrolysis, pure DL-*N*-benzoyl*allo*threonine in 93% yield. The oily ester was hydrolysed with 1 equiv. of cold sodium hydroxide; the free acid was purified *via* the 2-phenylethylamine salt (Carter and Risser, *J. Biol. Chem.*, **1941**, **139**, 255). The pure DL-*N*-benzoylthreonine so obtained was hydrolysed to DL-threonine in about 10% overall yield from hippuric acid.

It seemed desirable to find a convenient method of inverting the configuration of the hydroxyl group in the ester (VIII). This substance was converted into DL-N-*benzoyl*-O-p-*tosyl*allo*threonine ethyl ester* (IX) in 70% yield by reaction with *p*-tosyl chloride in dry pyridine. It appears that a portion of the ester (VIII) remained unattacked by the reagent even when an excess was used and the reaction time was increased considerably, but it is equally possible that a side reaction took place with formation of a labile compound, which was converted into (VIII) during the isolation procedure (compare Tipson, *J. Org. Chem.*, 1944, **9**, 235). The tosyl ester was obtained in two distinct crystal forms, according to the conditions of crystallisation. It was found possible to use the tosyl ester in the crude state. DL-*N*-Benzoyl*allo*threonine, as was expected, could not be converted into a tosyl derivative in the customary fashion, yielding instead 68% of 2-phenyl-4-ethylideneoxazol-5-one ("isomer I" of Carter, Handler, and Melville, *J. Biol. Chem.*, 1939, **129**, 359; see also Carter and Stevens, *ibid.*, 1940, **133**, 117).

The tosyl ester (IX) on treatment with potassium acetate in alcohol under the conditions described by Kenyon, Phillips, and Turley (*J.*, 1925, **127**, 399) for inversions of this type yielded a basic substance, forming a crystalline *picrate* and *hydrochloride* and the analytical data were in perfect agreement with the structure DL-trans-4-*carbethoxy*-2-*phenyl*-5-*methyl*-Δ^2-*oxazoline* (X). The configuration of this compound was demonstrated by hydrolysis with hydrobromic acid to pure DL-threonine.

It has been shown by Bergmann and Miekeley (*Z. physiol. Chem.*, 1924, **140**, 128) that the methyl ester of *N*-benzoylserine is readily converted into the corresponding oxazoline by the action of thionyl chloride and it seemed worth while to determine the configuration of the

product obtained from the ester (VIII) by this method. It was found that a smooth and quantitative inversion at the β-carbon atom took place as well as the expected ring closure

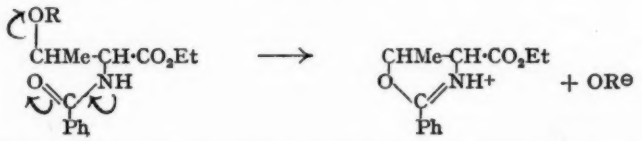


to give the *trans*-oxazoline (X), identical in all respects with the sample prepared from the tosyl derivative. The purity of the product was also confirmed by hydrolysis and microbiological assay of the amino-acid produced.

In order to show that inversion could also be carried out on a threonine derivative, a sample of crude ethyl α-benzamido-β-hydroxybutyrate, which was found to contain 33% of the DL-threonine derivative by microbiological assay of the amino-acid produced on hydrolysis, was treated with thionyl chloride to give a mixture of *cis*- and *trans*-oxazolines. The amino-acid produced on hydrolysis of this mixture was found to contain 70% of DL-threonine.

The hydrochloride of the oxazoline (X) rapidly absorbed water from the atmosphere and was converted into DL-O-*benzoylthreonine ethyl ester hydrochloride*. DL-2-Phenyl-Δ^2-oxazoline-4-carboxylic acid undergoes a similar ring fission to give DL-*O*-benzoylserine (Bergmann and Miekeley, *loc. cit.*).

It is considered that inversion and ring formation take place simultaneously in the above examples and the following mechanism [1] is proposed :



in which anionoid attack is carried out by the enolisable amide group. In the case of cyclisation with thionyl chloride, transient formation of an ester containing the group –O·SOCl is possible (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 188).

Microbiological assays, using *Strept. fæcalis*, were carried out in these laboratories using the method of Stokes, Gunness, Dwyer, and Caswell (*J. Biol. Chem.*, 1945, **160**, 35). A standard sample of pure DL-threonine was prepared by hydrolysis of a repeatedly recrystallised specimen of DL-*N*-formyl-*O*-methylthreonine (Carter and West, *Org. Synth.*, 1940, **20**, 101). DL-*allo*-Threonine was found to have no effect on the growth of *Strept. fæcalis* in the presence or absence of DL-threonine. Ammonium bromide, a likely contaminant in crude samples of amino-acid, was also without effect on the growth of the organism over a wide range of concentrations.

Experimental.

(M. p.s are corrected, unless otherwise stated.)

Sodium hippurate was prepared by dropwise addition of sodium (57·5 g.) dissolved in ethyl alcohol (800 ml.) to a boiling solution of hippuric acid (447·5 g.) in ethyl alcohol (2 l.) with stirring. The thick paste was filtered off and the mother liquors were evaporated to dryness to obtain a further small crop. The combined solids were dried first at 100° and then at 150°. The yield was 488 g. (97·5%). The substance was preserved in a tightly stoppered bottle because of its hygroscopic nature.

2-Phenyl-4-(1-hydroxyethylidene)oxazol-5-one.—Sodium hippurate (878 g.), β-picoline (1330 ml.), and acetic anhydride (1310 ml.) were placed in a 3½-gallon glazed-earthenware jar with 144 5/8″ glass balls, and the jar was closed with a calcium chloride tube in a rubber bung. The jar was turned on a roller mill for 2 hours. After 20 mins. the mixture had attained a temperature of about 40° and then gradually cooled. The dark green solution was separated, and the excess acetic anhydride decomposed by stirring with ethyl alcohol (750 ml.) at 30—35° with water cooling. Distilled water (7·5 l.) was added, and the solution acidified to Congo-red with dilute hydrochloric acid (1 : 1; 4·5 l.) while being

[1] The authors are indebted to Dr. J. W. Cornforth of the National Institute for Medical Research for this suggestion.

vigorously stirred. The green solid was filtered off and washed with distilled water (5 l.). The oxazolone was then dissolved in N-sodium hydroxide solution (4·5 l.) at 80°, charcoal (50 g.) was added, and the mixture stirred for 15 mins. The filtrate was cooled to room temperature and acidified (Congo-red) with dilute hydrochloric acid (1 : 1; *ca.* 1 l.) with vigorous stirring in order to obtain a more easily filterable product. The yellowish-pink product was dried in a desiccator; yield 739 g. (83·4%). The slightly impure 2-*phenyl*-4-(1-*hydroxyethylidene*)*oxazol*-5-*one* so obtained had m. p. 194—195° (decomp.) and was pure enough for further work. After sodium fusion the substance gave a weak positive test for sulphur.

The experiments given in the table were generally carried out in a similar manner, the yields quoted being for the crude products. Those experiments in which hippuric acid or 2-phenyloxazolone were used without addition of sodium acetate gave homogeneous solutions which were merely allowed to stand, though here it was found preferable to add sodium acetate immediately before working up to prevent slight losses in yield due to decomposition of the oxazolone by the alcohol used to remove excess acetic anhydride.

The oxazolone used for hydrogenations in aqueous solution, described below, was purified by chromatography of the sodium salt on alumina in acetone solution. The sodium salt was adsorbed on the alumina in 95% acetone and pigment removed by washing with 95% acetone. The column was then developed with 80% acetone. The oxazolone, purified in this way, formed yellow flattened needles from pure ethyl acetate, m. p. 198—199° (decomp.) (Found : C, 64·95; H, 4·6; N, 6·8. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5; N, 6·9%).

Benzamidoacetone.—The oxazolone (1 g.) was refluxed for 1 hour with water (50 ml.). The solid rapidly dissolved with effervescence (carbon dioxide) and gave a colourless solution. After evaporation to small bulk under reduced pressure, the ketone separated as colourless plates (yield 93%) and had m. p. 84° (Found : C, 67·7; H, 6·2; N, 7·7. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·3; N, 7·9%); Gabriel (*Ber.*, 1910, **43**, 1285) gives m. p. 85°. The 2 : 4-*dinitrophenylhydrazone* formed long golden needles from alcohol, m. p. 214—215° (Found : C, 53·9; H, 4·2; N, 19·4. $C_{16}H_{15}O_5N_5$ requires C, 53·8; H, 4·2; N, 19·6%).

Ethyl α-Benzamidoacetoacetate.—The oxazolone (10 g.) was refluxed for 2 hours with absolute alcohol (100 ml.); it slowly dissolved, and the solution was evaporated to dryness under reduced pressure. Crude ethyl α-benzamidoacetoacetate (yield quantitative) remained as a brown oil which gave a deep port-wine colour with aqueous-alcoholic ferric chloride. At 150°/10^{-4} mm. the ester distilled as a colourless oil; at the same time partial reconversion into the oxazolone took place, and this appeared in the distillate as a yellow precipitate (about 5—10% of the total). The oxazolone was removed by shaking the distillate with sodium hydrogen carbonate solution and ether, and the pure ester obtained by evaporation of the ether in a vacuum. This purified ester on redistillation behaved as before. The *semicarbazone* of the ester, formed in quantitative yield in aqueous solution, had m. p. 172—173° (decomp., uncorr.) (Found : C, 54·9; H, 5·7; N, 17·6; OEt, 14·3. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3; OEt, 14·7%).

Reaction of the Sodium Salt of Benzoyl-α-alanine with Acetic Anhydride.—The dry sodium salt (5 g.) was heated for 5 mins. at 100° with acetic anhydride (7·5 ml.). The solution became pale yellow and effervesced slightly. The mixture was rapidly cooled and diluted with dry ether (200 ml.) and, after thorough shaking, the white solid was filtered off and washed with dry ether. This solid contained no nitrogen and was probably sodium acetate (Found : Na, 26·4. Calc. : Na, 28·0%). The filtrate was evaporated in a vacuum, and the residue distilled, giving first a colourless oil, b. p. 62—63°/0·01 mm. (1·5 g.) (Found : C, 68·4; H, 5·6; N, 8·4. Calc. for $C_{10}H_9O_2N$: C, 68·5; H, 5·2; N, 8·0%). That this compound was 2-phenyl-4-methyloxazol-5-one was confirmed by hydrolysis to benzoyl-α-alanine, m. p. 162—164° (uncorr.), identical with an authentic specimen. The second fraction had b. p. 116—130°/0·01—0·03 mm. and was a pale yellow oil (1 g.). The 2 : 4-*dinitrophenylhydrazone* of *methyl* 1-*benzamidoethyl ketone*, prepared in 6N-hydrochloric acid from this fraction, formed pale yellow needles, m. p. 199—200° (uncorr.) (Found : C, 55·3; H, 4·8; N, 19·4. $C_{17}H_{17}O_5N_5$ requires C, 55·0; H, 4·6; N, 18·9%). This dinitrophenylhydrazone could conceivably have arisen also from 4-acetyl-2-phenyl-4-methyloxazol-5-one, if present in the high-boiling fraction, by ring fission and loss of carbon dioxide. That none of the required oxazolone was present was shown by the fact that the 2 : 4-dinitrophenylhydrazone prepared in alcoholic sulphuric acid was the same as the one prepared in aqueous solution and also by the following experiment. The high-boiling fraction (400 mg.) was refluxed for 2 hours with 2N-sulphuric acid (30 ml.), water (20 ml.), and phenylhydrazine (3 g.). The brown precipitate had m. p. 241—242° (decomp., uncorr.) after crystallisation from glacial acetic acid and gave no depression in m. p. with an authentic specimen of diacetyl phenylosazone. A negligible amount of carbon dioxide was produced during this reaction.

In a second experiment in which heating at 100° was continued for 1 min. and the reaction mixture worked up as before, the residue in the distilling flask solidified after removal of the first fraction. It was removed, rubbed with cold ether, and filtered off; after crystallisation from alcohol, the *compound* had m. p. 225—226° (decomp., uncorr.) (Found : C, 68·8; H, 5·2; N, 8·0. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·2; N, 8·0%). The ethereal filtrate yielded the same high-boiling fraction as in the first experiment.

2-*Phenyl*-4-(1-*hydroxypropylidene*)*oxazol*-5-*one.*—(a) Sodium hippurate was brought into reaction with propionic anhydride in much the same manner as with acetic anhydride to give a 76% yield. After crystallisation from pure ethyl acetate the 2-*phenyl*-4-(1-*hydroxypropylidene*)*oxazol*-5-*one* was obtained as clusters of pale yellow needles, m. p. 194—195° (decomp.), identical with the product described below.

(b) 2-Phenyloxazol-5-one (8 g.), dissolved in β-picoline (15 ml.), was cooled to 0° and propionyl chloride (4·1 g.) was added dropwise with vigorous shaking and continued cooling. After addition of ice and dilute hydrochloric acid, the oxazolone was filtered off and dried; yield 3·6 g. (34%). The purified substance had m. p. 194—195° as before (Found : C, 66·7; H, 5·1; N, 6·5. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·1; N, 6·45%).

2-*Phenyl*-4-*benzylideneoxazol*-5-*one.*—2-Phenyloxazol-5-one (4 g.) was mixed with β-picoline (5 ml.)

and benzaldehyde (2·6 ml.). The solution became hot after a few minutes and then solidified to a crystalline mass. After 3 hours, ice and excess of hydrochloric acid were added, and the solid was filtered off, washed with a small quantity of alcohol, and crystallised from benzene (yield 3·8 g.; 64%). The pale yellow needles had m. p. 166° and gave no depression in m. p. with an authentic specimen.

Hydrogenations of the Sodium Salt of the Oxazolone (I, R = Me).—(a) *α-Amino-β-hydroxybutyric acid.* The pure oxazolone (2 g.) was dissolved in 0·5 N-sodium hydroxide (20 ml.), Raney nickel (4 g.) added, and the solution shaken with hydrogen at room temperature and pressure. Absorption of hydrogen ceased after 20 hours when 4 mols. had been taken up. After filtration, N-hydrochloric acid (22 ml.) was added, and the solution evaporated to dryness under reduced pressure. The residue was warmed with alcohol (50 ml.) and filtered from sodium chloride, and aniline (3 ml.) was added to the filtrate which was allowed to stand overnight in the refrigerator. The amino-acid was filtered off, washed with alcohol, and dried at 100°; yield 650 mg. (54·5%), m. p. 234—235°, raised by crystallisation from 80% alcohol to 238—239°. Microbiological assay showed that this mixture contained about 7% of *dl*-threonine. A mixed m. p. with authentic α-amino-β-hydroxybutyric acid (Adkins and Reeve, *loc. cit.*; m. p. 230°) was 232°. It gave a deep blue colour with " ninhydrin " reagent (Found : C, 40·5; H, 7·4; N, 11·65. Calc. for $C_4H_9O_3N$: C, 40·3; H, 7·6; N, 11·8%). The use of less catalyst in this hydrogenation did not give satisfactory results.

(b) DL-N-*Benzyl*allo*threonine.* The oxazolone (10 g.) was dissolved in 0·5N-sodium hydroxide (110 ml.) and hydrogenated as before in the presence of Raney nickel (20 g.). After absorption of 1 mol. of hydrogen, the catalyst was removed and the filtrate acidified with concentrated hydrochloric acid (12·5 ml.). Unchanged starting material (6 g.) was removed, and the filtrate evaporated to small bulk in a vacuum. A small quantity of unidentified solid was filtered off and the evaporation continued to dryness. The isolation of the *amino-acid* then followed the procedure given in (a). The yield was 2·6 g. (63% on oxazolone used). It crystallised from water in tufts of long needles, m. p. 238° (decomp.), and gave no colour with " ninhydrin " reagent (Found : C, 63·0; H, 7·2; N, 6·7. $C_{11}H_{13}O_3N$ requires C, 63·2; H, 7·2; N, 6·7%).

The amino-acid (500 mg.) in a mixture of water (20 ml.) and N-sodium hydroxide (3 ml.) was hydrogenated as before in the presence of Raney nickel (1 g.). Absorption ceased after 12 hours when 1 mol. of hydrogen had been taken up. Slightly impure DL-*allo*threonine was isolated in the usual way in 70% yield and had m. p. 240—241° (decomp.) (Found : C, 40·4; H, 7·7; N, 11·5%).

(c) α-cyclo*Hexylmethylamino-β-hydroxybutyric acid.* The oxazolone (20 g.) was dissolved in 0·5N-sodium hydroxide (200 ml.) and hydrogenated at 85—90°/110 atm. in the presence of Raney nickel (20 g.). Absorption was complete in 2 hours. The product was worked up in the usual way and gave 7·5 g. of crude amino-acid, m. p. 232—238°. The solid was heated on the water-bath for an hour with water (15 ml.) and then cooled. After being filtered off, the solid was washed with water and dried at 100°; yield 4·2 g., m. p. 254° (decomp.). The filtrate was treated with hot alcohol (100 ml.). α-Amino-β-hydroxybutyric acid (3 g.) separated on cooling and had m. p. 231—232° (Found : C, 40·5; H, 7·6; N, 11·3%). Microbiological assay showed 19% of DL-threonine. The insoluble solid gave no colour with " ninhydrin " reagent. After several crystallisations from glacial acetic acid the α-cyclo*hexylmethylamino-β-hydroxybutyric acid* had m. p. 270° (decomp.) (Found : C, 61·3, 61·5; H, 9·8, 9·8; N, 6·3, 6·3. $C_{11}H_{21}O_3N$ requires C, 61·35; H, 9·8; N, 6·5%). In another experiment on the same scale carried out at 100—110°/125 atm. in the presence of Raney nickel (5 g.) the product consisted almost entirely of α-*cyclo*hexylmethylamino-β-hydroxybutyric acid. The toluene produced in one of these experiments was separated from the hydrogenation mixture by steam-distillation and had b. p. 110°. It was converted into *o*-(*p'*-toluoyl)benzoic acid, m. p. 139°, by the procedure of Underwood and Walsh (*J. Amer. Chem. Soc.*, 1935, **57**, 940) (Found : C, 74·8; H, 4·9. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%).

α-cyclo*Hexylmethylaminobutyric Acid.*—(a) α-*cyclo*Hexylmethylamino-β-hydroxybutyric acid (1 g.) was heated in a sealed tube with hydriodic acid (*d* 1·94; 7 ml.) and red phosphorus (0·17 g.) at 160° for 6 hours. After dilution to 200 ml. the solution was extracted three times with ether and then evaporated to dryness under reduced pressure. The residual syrup was dissolved in boiling water (50 ml.), a crystal of sodium sulphite was added, and then 2N-ammonia to faint alkalinity (litmus). After cooling, the *amino-acid* (600 mg., 65%) was filtered off, washed with water and alcohol, and then crystallised from glacial acetic acid. It formed fine needles, m. p. 300—302° (decomp. and sublimation; sealed tube) (Found : C, 66·4; H, 10·4; N, 7·2. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·6; N, 7·0%). The amino-acid (200 mg.) was suspended in dry alcohol (2·5 ml.) and dry hydrogen chloride passed in at room temperature to saturation. The solid rapidly dissolved. After standing overnight, the solvent was removed in a vacuum and the residue triturated with ether. The *hydrochloride* was filtered off, washed with ether, and crystallised from ethanol–ether, and had m. p. 211—213° (decomp.) (Found : Cl, 15·4. $C_{11}H_{22}O_2NCl$ requires Cl, 15·0%). The *ethyl ester hydrochloride* separated slowly from the ether washings but was preferably prepared by passing dry hydrogen chloride into a suspension of the amino-acid (200 mg.) in boiling alcohol (2·5 ml.) for 3 hours. The amino-acid was then completely esterified. The product, isolated in a similar way, formed fine needles from ethanol–ether and had m. p. 118—120° (Found : Cl, 13·4; OEt, 17·2. $C_{13}H_{26}O_2NCl$ requires Cl, 13·4; OEt, 17·1%).

(b) Cyano*cyclo*hexene (Ruzicka and Brugger, *Helv. Chim. Acta*, 1926, **9**, 399) was prepared from *cyclo*hexanone by the method used by Qudrat-i-Khuda and Ghosh (*J. Indian Chem. Soc.*, 1940, **17**, 19) for the 4-methyl homologue. The nitrile (21 g.), mixed with alcoholic ammonia (200 ml., saturated at room temp.) and Raney nickel (5 g.), was hydrogenated at 100—110°/125 atm. The reduction was complete in 30 mins., and after filtration of the catalyst the product was distilled. *cyclo*Hexylmethylamine distilled as a colourless oil, b. p. 160—162° (yield 16·2 g., 73%), giving a benzoyl derivative, m. p. 106—106·5°, and *N-cyclo*hexylmethylurea, m. p. 173·5° (Ruzicka and Brugger, *loc. cit.*, give m. p. 105—106° for the benzoyl derivative and m. p. 170—171° for the urea derivative of the amine prepared by chemical reduction of the nitrile).

α-Bromobutyric acid (2 g.), water (50 ml.), and the amine (5 g.) were mixed and heated on the steam-bath for 3 hours with occasional vigorous shaking. After cooling and neutralisation (litmus) with 2N-sulphuric acid, the amino-acid (1·6 g., 67%) was filtered off and purified as in (a). It had the same

m. p. as the specimen described above, and the hydrochloride (Found: Cl, 15·3; N, 5·9. Calc. for $C_{11}H_{22}O_2NCl$: Cl, 15·0; N, 5·9%) and ethyl ester hydrochloride (Found: Cl, 13·3; OEt, 17·1%) were also identical in m. p. and mixed m. p. with the samples described in (a).

DL-*Threonine.*—(1) *Hydrogenation of the keto-ester* (II, R = CO_2Et) *and separation of the isomeric products.* The oxazolone (220 g.) was refluxed for one hour with absolute alcohol (880 ml.); Raney nickel (15 g.) was then added, and the refluxing continued for 30 mins. The solution was filtered and hydrogenated at 100°/75—100 atm. in the presence of Raney nickel (50 g.). This required 1—3 hours. After removal of the catalyst the solution was evaporated to dryness in a vacuum to give 265 g. (97%) of crude hydroxy-ester. Hydrolysis of the crude substance so prepared with hydrobromic acid gave α-amino-β-hydroxybutyric acid in 64% yield from hippuric acid. The ester distilled at 100—110° (bath temp.)/10^{-6} mm. as a pale yellow oil which partly crystallised. Crystals obtained in this way were used to " seed " the crude ester as follows.

The ester (265 g.) was dissolved in dry ether (1·1 l.), " seeded ", and set aside at 0° for 3 days. The solid was filtered off and washed with absolute ether (220 ml.), the yield being about 160 g., m. p. 65—85°. It was crystallised first from a mixture of ethyl acetate (400 ml.) and light petroleum (b. p. 40—60°; 500 ml.) and then from a mixture of ethyl acetate (500 ml.) and light petroleum (b. p. 40—60°; 1 l.). The yield of DL-N-*benzoyl*allo*threonine ethyl ester* was 104 g. (38% based on the oxazolone), m. p 98·5—101·5° (Found: C, 62·2; H, 6·5. $C_{13}H_{17}O_4N$ requires C, 62·1; H, 6·8%). Microbiological assay of the DL-*allo*threonine produced on hydrolysis showed that less than 2% of DL-threonine was present. Mild alkaline hydrolysis by the method described below gave 93% of DL-*N*-benzoyl*allo*threonine, m. p. 177°; 2-phenylethylamine salt, m. p. 150—153°. These m. p.s are in good agreement with those recorded (West and Carter, *J. Biol. Chem.*, 1937, **119**, 109; Carter and Risser, *loc. cit.*).

The ethereal filtrate from the separation of the solid ester was evaporated to dryness under reduced pressure, and the yellow oil (108 g.) hydrolysed by shaking it with N-sodium hydroxide (430 ml.). The solution was filtered, neutralised with 1 equiv. of 5N-hydrochloric acid, treated with charcoal, filtered again, and evaporated to dryness under reduced pressure. The residue was dissolved in boiling alcohol (400 ml.) and filtered from sodium chloride, and 2-phenylethylamine (53 g.) added. The crystalline solid which separated on cooling was filtered off and recrystallised from alcohol (225 ml.). The m. p. of the pure 2-phenylethylamine salt was 161—162° (Carter and Risser, *loc. cit.*, give m. p. 159—162°) and the yield was 66 g. (18% based on the oxazolone). The salt was decomposed by dissolving it in water (100 ml.) at 60° and adding 2N-hydrochloric acid (144 ml.). After cooling in the refrigerator, the pure DL-*N*-benzoylthreonine (32 g.; 13% based on oxazolone) was filtered off and washed with ice-water. It had m. p. 145·5—146·5°. Hydrolysis with hydrobromic acid in the usual manner (see below) gave pure DL-threonine in about 12% yield from the oxazolone.

(2, a) *Walden inversion of the tosyl derivative* (IX). DL-*N*-Benzoyl*allo*threonine ethyl ester (240 g.) was dissolved in dry pyridine (850 ml.) and the mixture cooled to − 10°. *p*-Tosyl chloride (192 g., recryst.) was added, and the mixture shaken until the acid chloride had dissolved. The solution was kept at 0° for 3½ hours, and then poured, with stirring, on a mixture of concentrated hydrochloric acid (1·2 l.) and crushed ice (2·4 kg.). When solid, the product was filtered off, washed with 2N-hydrochloric acid (2 l.), then water (2 l.), and dried in a desiccator. The yield was 276 g. and the unused DL-*N*-benzoyl-*allo*threonine ethyl ester was recovered quantitatively from the washings by extraction with chloroform. DL-N-*Benzoyl*-O-p-*tosyl*allo*threonine ethyl ester* separated from light petroleum in fine needles, m. p. 82·5—83° (Found: N, 3·1; S, 8·2; OEt, 11·2. $C_{20}H_{23}O_6NS$ requires N, 3·5; S, 7·9; OEt, 11·1%), but when crystallised from ethyl acetate–light petroleum (b. p. 40—60°) it had m. p. 148·5—151·5° (Found: N, 3·4; S, 7·5; OEt, 10·1%). No difference in chemical behaviour, including the Walden inversion, could be detected in these samples.

The crude tosyl derivative (276 g.), fused and powdered potassium acetate (138 g.), and anhydrous ethyl alcohol (950 ml.) were mixed and refluxed for 2½ hours. The solution was evaporated and diluted with water (1·5 l.). The yellow oil was separated by ether extraction (3 × 500 ml.), and the ether dried and evaporated. The residual oil weighed 150 g. (36% based on the oxazolone). DL-trans-4-*Carbethoxy*-2-*phenyl*-5-*methyl*-Δ^3-*oxazoline* distilled as a colourless oil at 100°/10^{-5} mm. (Found: C, 67·1; H, 6·5; N, 6·1; OEt, 17·8. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5; N, 6·0; OEt, 19·3%). The *picrate* had m. p. 127·5° (Found: C, 49·6; H, 3·6; N, 12·2. $C_{19}H_{18}O_{10}N_4$ requires C, 49·4; H, 3·9; N, 12·1%). The *hydrochloride* formed colourless, tetragonal crystals, m. p. 117·5—118°, from methanol–ether, and rapidly absorbed moisture from the air, becoming opaque; accurate analytical figures were not obtained for it (Found: C, 57·1; H, 6·4; N, 4·9; Cl, 12·15. $C_{13}H_{16}O_3NCl$ requires C, 57·9; H, 6·0; N, 5·2; Cl, 13·15%).

(2, b) *Walden inversion of the ester* (VIII). DL-*N*-Benzoyl*allo*threonine ethyl ester (20 g.) was mixed with pure thionyl chloride (50 ml.). A vigorous evolution of gas took place and after one hour at room temperature, ether was added until a cloudiness was produced and the solution was treated with solid sodium hydrogen carbonate until there was no further effervescence. After filtration, washing of the residue with ether, and evaporation, a yellow oil (16 g.; 33% based on the oxazolone) remained. A sample was distilled in a high vacuum for analysis (Found: C, 67·05; H, 6·4; N, 6·2; OEt, 19·0%). The picrate had m. p. 127·5°, and the hydrochloride m. p. 118°. These derivatives gave no depression in a mixed m. p. determination with those described under (2, a). The identity of the two preparations of the oxazoline was confirmed by microbiological assay of the amino-acid produced on hydrolysis with hydrobromic acid. Both were found to be pure DL-threonine. A specimen of the oxazoline hydrochloride which had been standing in the laboratory atmosphere for a few days was crystallised from ethanol–ether and had m. p. 167°. This was found to be DL-O-*benzoylthreonine ethyl ester hydrochloride* (Found: C, 54·7; H, 6·4; N, 4·6; Cl, 11·9; OEt, 15·3. $C_{13}H_{16}O_4NCl$ requires C, 54·3; H, 6·3; N, 4·9; Cl, 12·3; OEt, 15·7%). The configuration of this substance was confirmed by microbiological assay of the amino-acid produced on hydrolysis. The hydrochloride, on treatment with aqueous sodium hydrogen carbonate, gave an oil, yielding a *picrate* as bright yellow needles, m. p. 140·5° (Found: C, 48·0; H, 4·25; N, 11·3. $C_{19}H_{20}O_{11}N_4$ requires C, 47·5; H, 4·2; N, 11·7%).

(3) *Hydrolysis.* The crude oxazoline ester (150 g.) was refluxed for 4 hours with 23% hydrobromic

acid (750 ml.) and cooled, the benzoic acid filtered off, and the residue evaporated to dryness under reduced pressure. The syrupy residue was dissolved in hot alcohol (750 ml.), and concentrated ammonia added to the hot solution in slight excess. After standing for 16 hours, the crude amino-acid (74 g.) was filtered off and recrystallised from a mixture of water (100 ml.) and ethyl alcohol (400 ml.). The yield of pure DL-threonine was 56 g. (26% based on the oxazolone). Other hydrolyses, mentioned above, were performed in a similar way.

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RESEARCH DIVISION, GLAXO LABORATORIES LTD.,
GREENFORD, MIDDLESEX.

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79. *The Periodic System of the Chemical Elements in Three Dimensions. (The "Five-Five System.")*

By A. G. OPPEGAARD.

A new classification of the chemical elements is presented. It is based on an arrangement of the elements in three dimensions, and has the following advantages: (1) Elements of related chemical properties but with different typical valency are collected into "planes". (2) Elements with same typical valency are collected into "groups". (3) Several weaknesses of the present forms of the periodic system are overcome. (4) It has a bearing on the geochemical distribution of elements.

THE Periodic System of the chemical elements has not yet reached a definite form generally acceptable to chemists and physicists. In textbooks and other literature one will hardly find two forms alike: the differences apply particularly to the composition of the homologous series.

Research on atomic constitution has had the Periodic System as its starting point and guide. Such research, however, was not satisfied with the Periodic System in its earlier forms, and this led to a new form relation—that of Thomson and Bohr. This new form consists mainly in that all homologous series are placed side by side, without any mutual relation. It does not seem probable that this form will be generally accepted. It is of little value to have all the series put side by side, and it is difficult to have the picture of the series in mind, when no practical connection or relation between them is established.

In the following a new classification of the chemical elements is described. It is characterised by an arrangement of the elements in all three dimensions, *i.e.*, in space and not in one "plane" as in the present forms. In the new form the elements fall into five different "planes" and five different "groups". It is proposed to designate the new form as the "five-five system"—5-5-S for short.

The Homologous Series.—A new rule according to which the homologous series may be determined more definitely than heretofore is proposed: *The Periodic System of elements consists of long and short homologous series. The short homologous series are composed of the typical heavy metals.* Accordingly, the series are:

Long series.		Short series.	
He–Ne–Ar–Kr–X–Rn	C–Si–Ti–Zr–Hf–(Th)	Cu–Ag–Au	Cr–Mo–W–(U)
Li–Na–K–Rb–Cs–87	N–P–As–Sb–Bi	Zn–Cd–Hg	Mn–43–Re
Be–Mg–Ca–Sr–Ba–Ra	O–S–Se–Te–Po	Ga–In–Tl	Fe–Ru–Os
B–Al–Sc–Y–La–Ac	F–Cl–Br–I–85	Ge–Sn–Pb	Co–Rh–Ir
		V–Nb–Ta–(Pa)	Ni–Pd–Pt

It will be seen that in the long series the basic properties of the elements will generally increase—and in the short series they will generally decrease—with increasing atomic weight. (Thallium is a paradox in its univalent state.)

One should perhaps consider antimony and bismuth as "heavy" metals, but usually they are not regarded as typical metals. In mineralogy they are more or less regarded as non-metals or metalloids.

In the new system it is not proposed to classify the rare earths in any further detail than in present systems: they all fall into the place of lanthanum. Thorium, protoactinium, uranium and subsequent "synthetic" elements are regarded as belonging to a new series of rare earths.

The Five-Five System.—A total picture of the 5-5-S is given in Fig. 1. Horizontal projections through the position of the inert-gas elements are seen in Fig. 2. All elements are connected to a curve in the order of the atomic number. The elements fall into 5 different groups, having the number 0, I, II, III, IV. A plane through the elements in each group will be at a right angle to the five planes:

Major positive plane (indicated by ≠)
Minor „ „ („ „ +)
Neutral „ „ („ „ 0)
Minor negative plane („ „ −)
Major „ „ („ „ =)

FIG. 1.

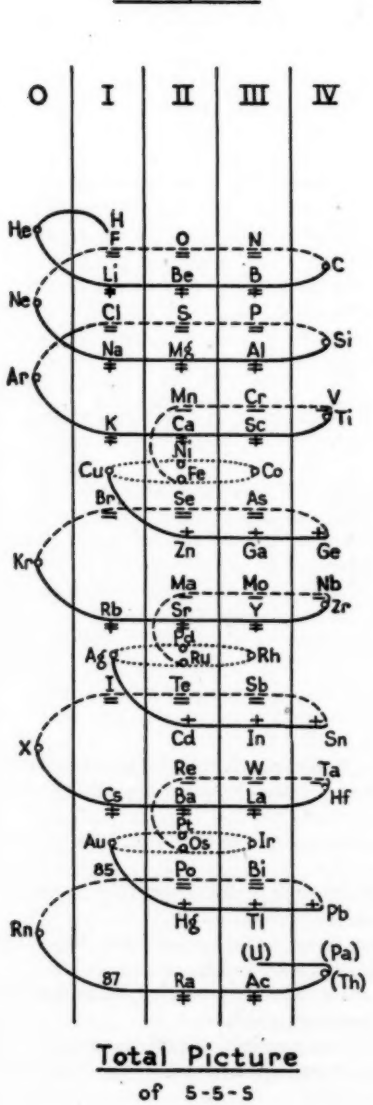
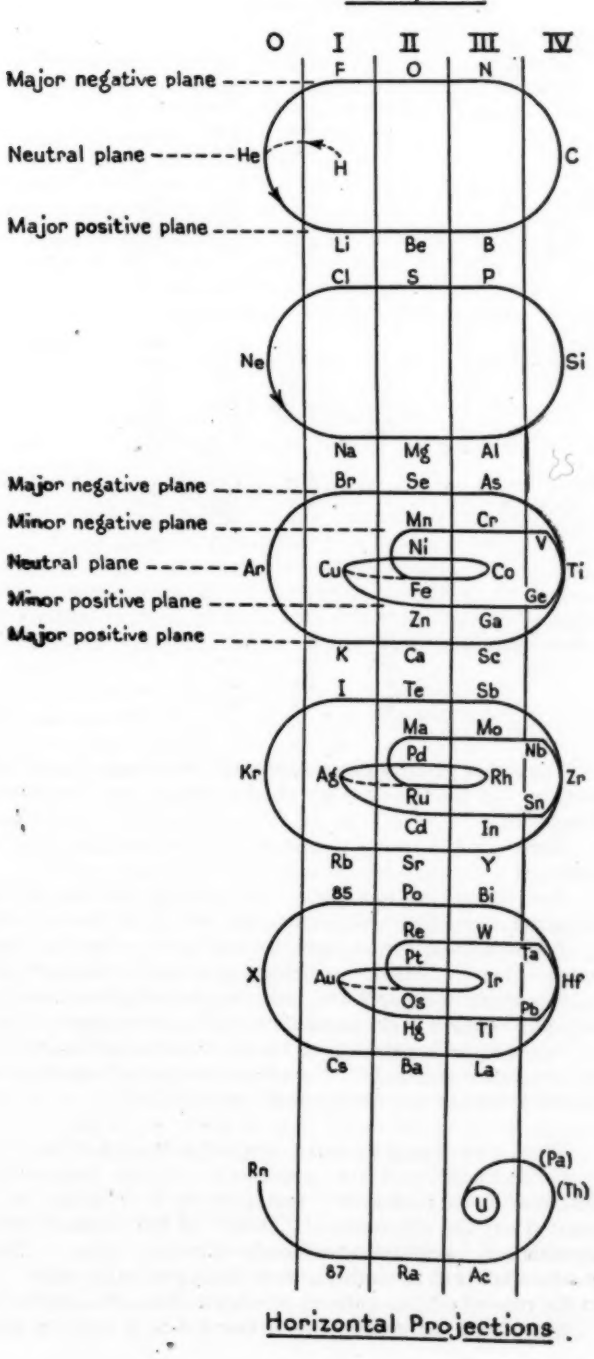


FIG. 2.



Every element (except a few rare elements) has now come into a group whose number corresponds to one of its typical valencies, and the valency corresponding to the group number is just the one in which most of the elements usually occur in Nature.

Hydrogen will form a top element of all three homologous series of Group I. A picture of the five planes and five groups is given in the table.

	Group number:					Plane:				
	0.	I.	II.	III.	IV.		Major positive.	Minor positive.	Neutral.	Minor negative.	Major negative.
Major positive plane		Li	Be	B		Group 0			He		
		Na	Mg	Al					Ne		
		K	Ca	Sc					Ar		
		Rb	Sr	Y					Kr		
		Cs	Ba	La					X		
		87	Ra	Ac					Rn		
						Group I	———		H		———
Minor positive plane			Zn	Ga	Ge		Li				F
			Cd	In	Sn		Na				Cl
			Hg	Tl	Pb		K		Cu		Br
							Rb		Ag		I
							Cs		Au		85
							87				
Neutral plane	He				C	Group II	Be				O
	Ne				Si		Mg				S
	Ar	Cu	Fe–Ni	Co	Ti		Ca	Zn	Fe–Ni	Mn	Se
	Kr	Ag	Ru–Pd	Rh	Zr		Sr	Cd	Ru–Pd	Ma	Te
	X	Au	Os–Pt	Ir	Hf		Ba	Hg	Os–Pt	Re	Po
	Rn				(Th)		Ra				
Minor negative plane			Mn	Cr	V	Group III	B				N
			Ma	Mo	Nb		Al				P
			Re	W	Ta		Sc	Ga	Co	Cr	As
				(U)	(Pa)		Y	In	Rh	Mo	Sb
							La	Tl	Ir	W	Bi
							Ac			(U)	
Major negative plane		F	O	N		Group IV			C		
		Cl	S	P					Si		
		Br	Se	As				Ge	Ti	V	
		I	Te	Sb				Sn	Zr	Nb	
		85	Po	Bi				Pb	Hf	Ta	
									(Th)	(Pa)	

The major positive plane comprises the alkali metals, the alkaline-earth metals, and the earth metals. In the terminology of mineralogy, the " rock-forming " base elements are all found in this plane.

The " ore "-forming elements, *i.e.*, the heavy metals, are found in the three middle planes, namely :

The minor positive plane, comprising the heavy metals which form weakly positive components in chemical compounds, and which have a low melting point.

The neutral plane, comprising the inert-gas series, the precious-metal series, and the C–Th series : they lie between positive and negative elements in the sense of 5–5-S.

The minor negative plane, comprising the typical heavy metals, which, as oxides, form weakly negative radicals in chemical compounds; these have a high melting point.

In the major negative plane those elements are found which form strongly negative components in chemical compounds. The plane comprises the typical acid-forming elements. The elements of this plane are non-metals and " metalloids ".

From a petrographic and mineralogical point of view the 5–5-S has certain advantages.

Goldschmidt and his co-workers, in their famous treatises " Laws on the Geochemical Distribution of Elements " (particularly in Treatise No. VIII, Oslo, 1927, pp. 77—80), have pointed out the difference of " state " of the atoms in crystals of NaCl-type, as compared with crystals of wurtzite–zinc blende–diamond type. The conclusion is based upon exact measurements of atom distance in these simple crystals. There are, however, certain exceptions to the rule which the authors point out (TiC, ZrC, MgTe, AlSb).

Seen from the standpoint of the 5–5-S, it may be concluded that the crystals whose atom

distance follows what the authors call the rule of the NaCl type (decreasing distance with increasing valency) have their positive component in the *major positive* plane. The crystals whose atom distance follows what the authors call the rule of wurtzite–zinc blende–diamond type (constant distance, independent of valency) have their positive component in the *minor positive* or the *neutral* plane.

The apparent exceptions to the rule which the authors point out, basing their conclusion on the crystal form, are not exceptions when seen from the standpoint of the 5–5-S. The main consideration is not the crystal form, but the plane to which the positive atom belongs.

This conclusion is of considerable practical importance. As in these simple crystals the elements are in different " state ", one cannot expect that elements of the major positive plane and elements of the heavy metals planes will be associated in crystals of this type. Taking, for instance, zinc blende (ZnS), one finds scarcely any elements of the major positive plane in this mineral. Many other heavy metals of the minor positive plane (Cd, Hg, In, Ga, Tl, Sn, Pb) and of the neutral plane (Fe, Ag, Au) are, however, found in zinc blende.

Similarly, in sodium chloride one rarely finds elements of the heavy metal planes, but very often other elements of the major positive plane : K, Ca, etc.

In more complicated minerals, like compounds of two or more oxides (as MgO,SiO_2 and FeO,SiO_2), the " state " of the positive element (Mg and Fe) appears to be the same. In very many minerals one finds isomorphous mixtures and replacements of elements having the same valency and belonging to identical group of 5–5-S, but to different planes. This fact can usually be traced back to similarity in ionic (or atomic) radii.

Isomorphous mixtures and replacements in minerals are well known of the following groups of elements.

Bivalent elements (of Group II of 5–5-S), as Mg, Ca, Ba, Zn, Cd, Fe, Ni, Mn.

Tervalent elements (of Group III of 5–5-S) as Al, Sc, Y, La (and other rare earths), Ga, In, Tl, Cr, U.

Quadrivalent elements (of Group IV of 5–5-S) as Si, Ti, Zr, Hf, Th, Sn, V, Nb, Ta.

Vanadium in minerals is usually regarded as being in the ter- or quinque-valent state. It is, however, probable that it enters many minerals in the quadrivalent state, in view of the simultaneous presence of bi- and ter-valent iron in many vanadium-containing minerals (particularly titanium minerals). The quadrivalency of vanadium is so strong that some compounds of V_2O_5 spontaneously lose oxygen to form compounds containing V_2O_4. Niobium and tantalum are usually regarded as typical quinquevalent elements, but they have also a distinct quadrivalency.

The natural parageneses of elements of the planes are interesting.

Elements of the *major positive* plane are associated in very many rock-forming minerals. In sea-water salts elements of this plane form typical positive components.

The parageneses of metals of the *minor positive* plane (Zn, Cd, Hg, Ga, In, Tl, Ge, Sn, Pb) are well known.

The heavy metals of the *neutral* plane (Fe, Co, Ni, Cu, Ru, Rh, Pd, Ag, Os, Ir, Pt, and Au) are a typical family. In precious metals found in Nature, one has always a good chance of finding all heavy metals of the neutral plane. Likewise, in certain FeS ores containing nickel one finds practically all other heavy metals of the neutral plane.

Elements of the *minor negative* plane (V, Nb, Ta, Mo, W, Mn, Re) show a distinct paragenesis. In columbite, for instance, one usually finds all these elements—and further some of the elements of 4th *group* of 5–5-S, namely, Ti and Sn besides Nb, V, and Ta.

Elements of the *major negative* plane form negative components in minerals, and are often associated. In sea-water salts elements of this plane form the typical negative components.

The above facts suggest the following conclusion : Elements associated in Nature will usually belong to the same group, or to the same plane of the 5–5-S. When they belong to the same plane, the natural parageneses are a consequence of similarity in chemical behaviour. When they belong to the same group the parageneses follow from similarity in ionic (or atomic) radii. In many minerals both types of relationship are expressed simultaneously.

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TITAN CO. A/S, FREDRIKSTAD, NORWAY. [*Received, January 14th*, 1947.]

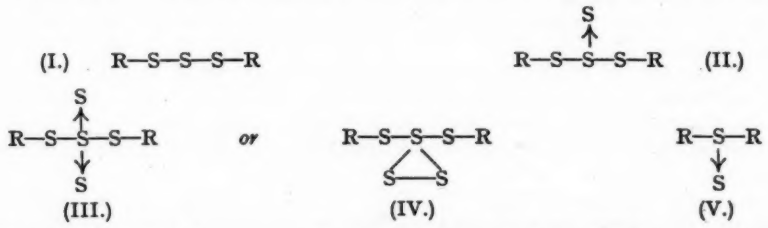
80. *The Structure of Certain Polysulphides and Sulphonyl Sulphides. Part I. A Preliminary X-Ray Survey.*

By I. M. Dawson, A. McL. Mathieson, and J. Monteath Robertson.

A survey of unit cell and space-group data is given for diphenyl and di-*p*-tolyl disulphide, 2:2′-di-iododiethyl trisulphide, 2:2′-dichlorodiethyl trisulphide, diphenyl and di-*p*-tolyl disulphone, bisphenyl- and bis-*p*-tolyl-sulphonyl sulphide, bisphenyl- and bis-*p*-tolyl-sulphonyl trisulphide. At least five, and possibly six of these molecules display a two-fold axis of symmetry in the crystal. This element is present in all the molecules which contain groups of three or more sulphur atoms, from which it is clear that there is no possibility of side co-ordination to a single sulphur atom. In all cases the evidence is in favour of extended zigzag sulphur chains. Preliminary estimates of molecular orientation in the crystal lattice are given for several of the compounds, and those most suitable for further detailed *X*-ray analyses are indicated.

Exact knowledge of configuration, bond distances, and valency angles in molecules which involve groups or chains of sulphur atoms is rather meagre. Some of the well-known crystalline modifications of the element itself have received fairly detailed examination. In the stable orthorhombic form the S_8 molecule has a regular, puckered-ring structure, the S–S distance being 2·12 A. and the S–S–S angle 105·4° (Warren and Burwell, *J. Chem. Physics*, 1935, **3**, 6). This configuration appears to hold, although associated with rather large thermal vibrations, in the vapour phase (Lu and Donohue, *J. Amer. Chem. Soc.*, 1944, **66**, 818), but an open-chain form has been established for plastic sulphur (Meyer and Go, *Helv. Chim. Acta*, 1934, **17**, 1081).

Determination of the molecular configuration of the organic polysulphides by chemical methods has been rendered exceedingly difficult by the instability of these compounds, the higher polysulphides readily decomposing to give free sulphur and a lower polysulphide. In previous structural investigations both parachor and viscosity measurements have been utilized. From the former, Baroni (*Atti R. Accad. Lincei*, 1931, **14**, 28) found support for the idea that tri-, tetra-, and penta-sulphides contain 3 sulphur atoms in a linear arrangement (I), with the additional sulphur atoms side-co-ordinated in the case of tetra- and penta-sulphides, (II)—(IV). Bezzi (*Gazzetta*, 1935, **65**, 693), on the other hand, obtained viscosity measure-



ments which indicated that in mono-, di-, and tetra-sulphides with the same terminal alkyl groups the molecular length is constant. He concluded, therefore, that in all the polysulphides there is a marked tendency to side-co-ordination and he formulated the disulphides as (V).

It is thus a point of considerable interest to determine whether sulphur does in fact show a tendency to form co-ordinate links in the polysulphides. In the various molecular forms of the element itself there is as yet no evidence of any such tendency. The present work was therefore initiated partly in an effort to resolve the inconsistencies in the reported results from parachor and viscosity measurements given by Baroni and by Bezzi (*locc. cit.*).

With regard to the polythionates, the structures of the dithionate and trithionate ions have been studied by a number of workers in various inorganic salts. In the dithionate ion, $S_2O_6^{--}$, the two sulphur atoms lie on a three-fold symmetry axis, about 2·08 A. apart, and about each sulphur atom the three oxygen atoms and the other sulphur atom are arranged tetrahedrally, with a sulphur–oxygen distance of about 1·50 A. (Huggins and Frank, *Amer. Min.*, 1931, **16**, 580; Helwig, *Z. Krist.*, 1932, **83**, 485; Huggins, *ibid.*, 1933, **86**, 384; Barnes and Wendling, *ibid.*, 1938, **99**, 153). The metabisulphite (pyrosulphite) ion, $S_2O_5^{--}$, is similar in structure to the dithionate ion, but with one oxygen atom removed (Zachariasen, *Physical Rev.*, 1932, **40**, 923). In the trithionate ion, $S_3O_6^{--}$, the terminal SO_3 groups are again approximately tetrahedral and the bonds to the central linking sulphur atom make a S–S–S valency angle of about 103°. The sulphur–oxygen distances are about 1·50 A., and sulphur–sulphur about 2·15 A.

(Zachariasen, *Z. Krist.*, 1934, **89**, 529; Ketelaar and Sanders, *J. Chem. Physics*, 1936, **4**, 621). Morphological and space-group data have been given for potassium tetrathionate (Tunell, Merwin, and Ksanda, *Amer. J. Sci.*, 1938, *A*, **35**, 361) but structural details appear to be unknown for the higher polythionates.

Some fairly detailed *X*-ray studies, with Patterson and Fourier projections, have been made by Toussaint (*Bull. Soc. roy. Sci. Liége*, 1944, **13**, 111, 163) of *pp'*-dibromodiphenyl sulphide and *pp'*-dibromodiphenyl sulphone. The results are somewhat obscured by effects due to the heavy atoms, but in the sulphone an approximately tetrahedral distribution of bonds about the central sulphur is established, with a rather uncertain sulphur–oxygen distance of 1·54 A. The planes of the benzene rings are found to lie at right angles to the plane containing Br . . S . . Br. In both molecules a two-fold axis of symmetry passes through the central sulphur. Further space-group data for di-*p*-tolyl sulphide, phenyl α-naphthyl sulphide, and nitro-derivatives are given by the same author (*ibid.*, 1943, **12**, 153, 533).

The present paper gives a survey of unit cell and space-group data for several crystalline organic di- and tri-sulphides, two isomorphous disulphones (so-called dithionates), and some sulphonyl sulphides and sulphonyl trisulphides (so-called trithionates and pentathionates). This preliminary work is necessary in order to select the compounds most suitable for the detailed *X*-ray analyses to be described in subsequent papers. There was also a hope that some elements of molecular symmetry might be detected which would limit the possible structural types as well as simplify subsequent calculations. This has proved to be the case, for a two-fold axis of symmetry has been established in five of the molecules and is probably present in a sixth.

Diphenyl Disulphide, $C_{12}H_{10}S_2$.—*Crystal data.* M, 218·3; m. p. 59°; d, calc. 1·336, found 1·338; orthorhombic hemihedral, $a = 8·11 \pm 0·02$, $b = 23·67 \pm 0·03$, $c = 5·61 \pm 0·02$ A. Absent spectra, ($h00$) when h is odd, ($0k0$) when k is odd, ($00l$) when l is odd. Space-group, D_2^4–$P2_12_12_1$. Four molecules per unit cell. Molecular symmetry, none required. Volume of the unit cell, 1077 A.^{3}. Absorption coefficient for *X*-rays ($\lambda = 1·54$), $\mu = 40·7$ per cm. Total number of electrons per unit cell = F(000) = 456.

Good crystals in the form of long needles or laths, with prominent development of (110) faces, are easily obtained by crystallisation from alcohol. Previous crystallographic studies are recorded by Groth ("Chemische Kristallographie," Leipzig, 1919, **5**, 33), and more recently an *X*-ray investigation has been made by Egartner, Halla, and Schachel (*Z. physikal. Chem.*, 1932, *B*, **18**, 189), whose determination of the unit cell and space-group are in good agreement with our data.

Neither cell dimensions nor space-group data provide any special clue to the molecular arrangement. Molecules of presumably similar shape exist in the stilbene and *trans*-azobenzene crystals (Robertson and Woodward, *Proc. Roy. Soc.*, 1937, *A*, **162**, 568; de Lange, Robertson, and Woodward, *ibid.*, 1939, *A*, **171**, 398), but apart from the similarity of the b axis in these crystals (5·70 and 5·77 A.) to the c axis in diphenyl disulphide (5·61), there is little to be gained from this comparison.

Di-p-*tolyl Disulphide*, $C_{14}H_{14}S_2$.—*Crystal data.* M, 246·4; m. p. 46°; d, calc. 1·240, found 1·246; monoclinic hemihedral, $a = 7·72 \pm 0·02$, $b = 5·76 \pm 0·02$; $c = 14·81 \pm 0·03$ A., $\beta = 95·4° \pm 0·2°$. Absent spectra, ($0k0$) when k is odd. Space-group, C_2^2–$P2_1$ (or C_{2h}^2–$P2_1/m$). Two molecules per unit cell. Molecular symmetry, none required (centre in $P2_1/m$). Volume of the unit cell = 656 A.^{3}. Absorption coefficient for *X*-rays ($\lambda = 1·54$), $\mu = 34·1$ per cm. Total number of electrons per unit cell = F(000) = 260.

Well-formed, needle-shaped crystals, with (001) prominently developed, and (100) and (011) also present, are readily obtained from alcohol. There is cleavage parallel to (100) and (010). A slight positive pyroelectric effect was noted, indicating the space-group of lower symmetry, $P2_1$.

As in the case of diphenyl disulphide, neither cell dimensions nor symmetry provides any obvious clue to the molecular arrangement. A Patterson synthesis of intensity data from the ($h0l$) zone of reflections was prepared, and this indicated that the long axes of the molecules lie approximately parallel to the (010) plane and that their distance apart in projection along the b axis is about 4 A. The complexity of the structure made it impossible to recognise the peaks due to the interaction of bonded atoms, and it would appear that further progress must be made by trial and error methods.

2 : 2'-*Di-iododiethyl Trisulphide*, $C_4H_8I_2S_3$.—*Crystal data.* M, 406·1; m. p. 110°; d, calc. 2·521, found 2·478; tetragonal trapezohedral, $a = b = 6·01 \pm 0·02$, $c = 29·40 \pm 0·04$ A. Absent spectra, ($h00$) when h is odd, ($0k0$) when k is odd, ($00l$) except when $l = 4n$. Space-

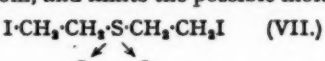
group D_4^4–$P4_12_1$ (or D_4^8–$P4_32_1$). Four molecules per unit cell. Molecular symmetry, two-fold axis perpendicular to (110). Volume of the unit cell, 1162 A.^{3}. Absorption coefficient for X-rays ($\lambda = 1{\cdot}54$), $\mu = 551{\cdot}2$ per cm. Total number of electrons per unit cell = F(000) = 744.

Thin, flat plates are readily obtained from alcohol–benzene, with (001) prominently developed; (011) and (101) are also displayed. A distinct tendency for cleavage parallel to (100) was noted.

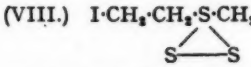
The space-group data are free from ambiguity (D_4^8 is merely the enantiomorph of D_4^4) and require each molecule to possess an exact two-fold axis of symmetry. This definitely excludes structure (IX) with side co-ordination to a single sulphur atom, and limits the possible molecular

(VI.) $I{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}S{\cdot}CH_2{\cdot}CH_2I$

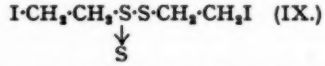
(VII.)



(VIII.)



(IX.)



configurations to (VI), (VII), or (VIII). Of these, (VI) appears to be the most probable from dimensional considerations based on the known covalent radii for carbon, sulphur, and iodine. These are in favour of an extended zigzag chain type of structure, lying in the direction of the c axis. Such a model is supported by a study of the X-ray intensities, particularly the very strong (008) and (106) reflections. These considerations lead to a full analysis of the structure, which will be described in a subsequent paper.

2 : 2′-*Dichlorodiethyl Trisulphide*, $C_4H_8Cl_2S_3$.—*Crystal data.* M, 223·2; m. p. 27°; d, calc. 1·491, found 1·494; orthorhombic, $a = 5{\cdot}47 \pm 0{\cdot}03$, $b = 8{\cdot}01 \pm 0{\cdot}03$, $c = 22{\cdot}5 \pm 0{\cdot}04$ A. Absent spectra, ($h00$) when h is odd, ($00l$) except when $l = 4n$. No data obtained about ($0kl$), ($0k0$), or ($hk0$). Space-group, possibly D_2^4–$P2_12_12_1$. Four molecules per unit cell. Molecular symmetry, none required from space-group considerations, but the quartering of ($00l$) indicates a two-fold axis. Volume of the unit cell, 998 A.^{3}. Total number of electrons per unit cell = F(000) = 456.

Unfortunately, this compound can only be crystallised with great difficulty, and the high volatility of the few single crystals obtained did not permit of a complete analysis. The cell dimensions show some resemblance to those of the di-iodo-compound, and the apparent quartering of the ($00l$) series of reflections is significant. This in effect indicates an identity of the electron-density distribution in the unit cell over each quarter of the c axial line projection, and with four molecules in a unit cell of this cross-section implies a two-fold axis of symmetry in the molecule. These results favour the conclusion that the molecular configuration of the dichloro-compound is similar to that of the di-iodo-compound.

Diphenyl Disulphone, $C_{12}H_{10}O_4S_2$.—*Crystal data.* M, 282·2; m. p. 193°; d, calc. 1·472, found 1·482; triclinic, $a = 6{\cdot}31 \pm 0{\cdot}02$, $b = 7{\cdot}90 \pm 0{\cdot}03$, $c = 8{\cdot}40 \pm 0{\cdot}04$ A., $\alpha = 57°\ 48'$, $\beta = 112°\ 41'$, $\gamma = 116°\ 17'$; $d_{100} = 5{\cdot}54$, $d_{010} = 6{\cdot}36$, $d_{001} = 6{\cdot}97$ A. No absent spectra. Space-group, C_1^1–$P1$ or C_i^1–$P\bar{1}$. One molecule per unit cell. Molecular symmetry, none in $P1$, centre in $P\bar{1}$. Volume of the unit cell, 316 A.^{3}. Absorption coefficient for X-rays ($\lambda = 1{\cdot}54$), $\mu = 38{\cdot}9$ per cm. Total number of electrons per unit cell = F(000) = 146.

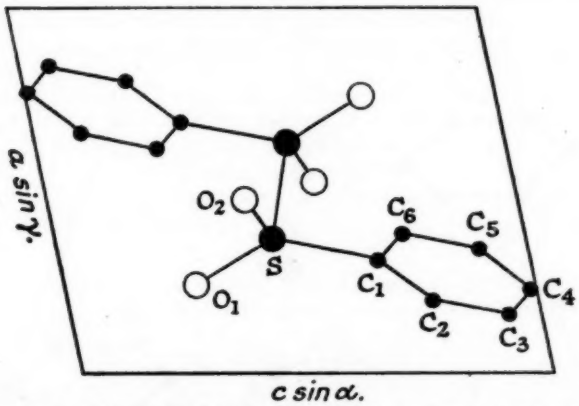
From glacial acetic acid well-formed prisms are obtained, showing (100), (010), (001), and (110) faces. No molecular symmetry can be deduced from space-group data, although a centre of symmetry is possible, and dipole-moment measurements (Oesper and Smyth, *J. Amer. Chem. Soc.*, 1942, **64**, 768) suggest a tetrahedral grouping about two sulphur atoms joined by a single bond with the possibility of rotation, which is consistent with a centrosymmetric molecule in the crystal. We have carried out tests for piezo- and pyro-electric effects and have obtained no definitely positive results, which is again in favour of a centrosymmetric structure.

Comparison of dimensions with the isomorphous ditolyl compound, described below, indicates that the benzene rings must lie fairly close to the c axis. Inspection of the zero layer line moving-film photographs of ($0kl$), ($h0l$) and ($hk0$) supports this conclusion and further indicates that the S–S line is lying at a small angle to the b axis since (010) is strong, (020) very strong, and (030) medium. The ($h0l$) series more readily defines the general lay-out of the molecule, with (001) very strong, (002) strong, (003) strong, (004) strong, and (100) very strong, (200) weak, (300) weak, (400) strong, (500) strong. The deductions from this intensity distribution are in accordance with the general arrangement shown in Fig. 1. The structure as a whole probably bears a close resemblance to that of the disulphonyl sulphide described below (Fig. 2). It seems likely that the assumption of a centre of symmetry in the molecule is justified and may lead to a fully detailed structure determination.

Di-p-tolyl Disulphone, $C_{14}H_{14}O_4S_2$.—*Crystal data.* *M*, 310·2; m. p. 206° (decomp.); *d*, calc. 1·409, found 1·422; triclinic, $a = 7{\cdot}21 \pm 0{\cdot}03$, $b = 8{\cdot}14 \pm 0{\cdot}03$, $c = 9{\cdot}97 \pm 0{\cdot}04$ A., $\alpha = 56°\ 2'$, $\beta = 128°\ 19'$, $\gamma = 122°\ 56'$; $d_{100} = 5{\cdot}39$, $d_{010} = 6{\cdot}43$, $d_{001} = 7{\cdot}37$ A. No absent spectra. Space-group, C_1^1–$P1$ or C_i^1–$P\bar{1}$. One molecule per unit cell. Molecular symmetry, none in $P1$, centre in $P\bar{1}$. Volume of the unit cell = 363 A.^{3}. Absorption coefficient for *X*-rays ($\gamma = 1{\cdot}54$), $\mu = 34{\cdot}5$ per cm. Total number of electrons per unit cell = F(000) = 162.

The crystal habit is similar to that of the diphenyl compound, and the data show that they are isomorphous. In the ditolyl crystal the *c* axis has expanded from 8·40 to 9·97 A. and the β angle has increased from 112° 41′ to 128° 19′, which is consistent with an orientation of the benzene rings similar to that shown in Fig. 1. There is further a close similarity in the distribution of intensities for the (*h*00) and the (0*k*0) reflections in the two crystals, whereas the (00*l*) reflections are modified by the expansion of the *c* axis and the enlargement of the angle β. A complete structure analysis of this crystal again appears to be feasible.

FIG. 1.

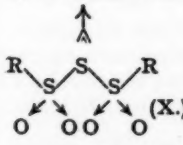


Approximate orientation of diphenyl disulphone molecule in the unit cell.

Bisphenylsulphonyl Sulphide, $C_{12}H_{10}O_4S_3$.—*Crystal data.* *M*, 314·3; m.p. 133°; *d*, calc. 1·618, found 1·583; monoclinic prismatic, $a = 15{\cdot}88 \pm 0{\cdot}06$, $b = 5{\cdot}52 \pm 0{\cdot}01$, $c = 15{\cdot}88 \pm 0{\cdot}06$ A., $\beta = 112{\cdot}9°$. Absent spectra, (*hkl*) when $h + l$ is odd, (*h*0*l*) when *h* is odd or when *l* is odd. Space-group, C_{2h}^6–$A2/a$ (or C_s^4–Aa). Four molecules per unit cell. Molecular symmetry, two-fold axis (or centre) in $A2/a$ (none in Aa). Volume of the unit cell, 1282 A.^{3}. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$), $\mu = 53{\cdot}3$ per cm. Total number of electrons per unit cell = F(000) = 648.

Further crystallographic data are given by Groth (*loc. cit.*, 1919, **5**, 38) who describes the crystal as orthorhombic bisphenoidal, and dipole-moment measurements are reported by Christiansen (*Z. Elektrochem.*, 1928, **34**, 638). From glacial acetic acid, lath-like crystals elongated along the *b* axis are obtained which show (100) and (001) faces. The crystal class appears to be prismatic and the space-group C_{2h}^6, but it is impossible to exclude the space-group of lower symmetry C_s^4 from a study of the halvings alone.

In the structure analysis the higher symmetry of C_{2h}^6 was first assumed and later justified by a detailed study of the intensities. With four molecules in the unit cell this space-group requires a two-fold element of molecular symmetry which must be either a centre or a two-fold axis parallel to the *b* crystal axis. A centre of symmetry is clearly incompatible with any reasonable molecular structure for the group under discussion, while the two-fold axis is consistent with the expected structure (X) with a tetrahedral distribution of bonds about the two outer sulphur atoms. This conclusion has now been confirmed by a more detailed analysis which will be described in a subsequent paper.



(X.)

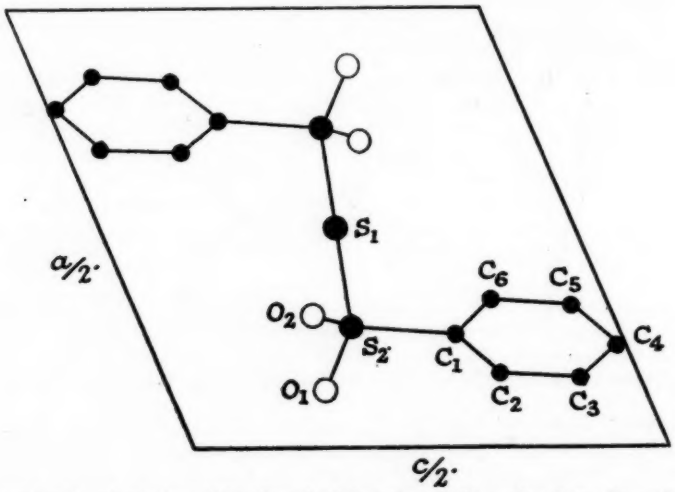
The general disposition of the molecule in the asymmetric crystal unit is shown in Fig. 2, the line $S_2C_1C_4$ being close to the direction of the *c* axis, and giving rise to a very strong (400) reflection. The (20$\bar{4}$), 20$\bar{8}$), and (20$\bar{8}$) are also strong, while the (002) series falls off normally. The two-fold axis of symmetry is normal to the plane of the diagram and passes through the central sulphur atom. The packing of the molecules in the crystal is an interesting

one, and is such that a fairly close approach is made between the oxygen atoms of the SO_2 groups and the benzene rings of neighbouring molecules.

Bis-p-*tolylsulphonyl Sulphide*, $C_{14}H_{14}O_4S_3$.—*Crystal data.* M, 342·3; m. p. 138°; d, calc. 1·430, found 1·427; monoclinic prismatic, $a = 16{\cdot}50 \pm 0{\cdot}05$, $b = 5{\cdot}85 \pm 0{\cdot}01$, $c = 18{\cdot}88 \pm 0{\cdot}03$ A., $\beta = 119{\cdot}9°$. Absent spectra, (hkl) when $h + l$ is odd, ($h0l$) when h is odd or when l is odd. Space-group, C_{2h}^6–$A2/a$ (or C_s^4–Aa). Four molecules per unit cell. Molecular symmetry, two-fold axis (or centre) in $A2/a$ (none in Aa). Volume of the unit cell, 1581 A.^{3}. Absorption coefficient for X-rays ($\lambda = 1{\cdot}54$), $\mu = 35{\cdot}7$ per cm. Total number of electrons per unit cell = F(000) = 712.

Further crystallographic data are recorded by Groth (*op. cit.*). The crystals are isomorphous with the phenyl analogue and the molecular symmetry is the same, *i.e.*, a two-fold axis parallel to the b crystal axis. From the expansion of the β angle from 112·9° to 119·9° and the increase in the c axis from 15·88 to 18·88 A., it may be concluded that the benzene rings lie closely parallel to the c axis as in Fig. 2. The ($h00$) series of reflections have a distribution of intensities almost the same as those of the diphenyl compound, and the general distribution of

FIG. 2.



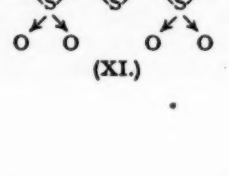
Approximate orientation of bisphenylsulphonyl sulphide molecule in the unit cell.

intensities in the ($h0l$) zone shows that the structure is very similar to that of that compound as regards its disposition in the unit cell.

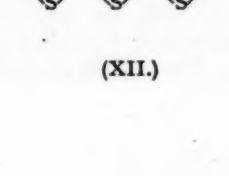
Bisphenylsulphonyl Trisulphide, $C_{12}H_{10}O_4S_5$.—*Crystal data.* M, 378·4; m. p. 103°; d, calc. 1·584, found 1·582; tetragonal trapezohedral, $a = 7{\cdot}74 \pm 0{\cdot}02$, $c = 26{\cdot}29 \pm 0{\cdot}05$ A. Absent spectra, ($h00$) when h is odd, ($0k0$) when k is odd, ($00l$) except when $l = 4n$. Space-group, D_4^4–$P4_12_1$ (or D_4^8–$P4_32_1$). Four molecules per unit cell. Molecular symmetry, two-fold axis perpendicular to (110). Volume of the unit cell, 1575 A.^{3}. Absorption coefficient for X-rays ($\lambda = 1{\cdot}54$), $\mu = 66{\cdot}7$ per cm. Total number of electrons per unit cell = F(000) = 776.

From glacial acetic acid the compound crystallises in small bipyramids showing (101) and (011) faces. Further crystallographic measurements are recorded by Groth (*op. cit.*, p. 39) and dipole moment measurements by Christiansen (*loc. cit.*).

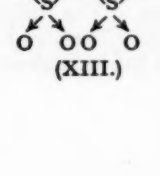
The space-group data show clearly that the molecule must possess an exact two-fold axis of symmetry perpendicular to the (110) crystal plane. This limits the possible structures for the compound to (XI), (XII), or (XIII), and of these (XI) is certainly the most probable on chemical grounds; (XII) would involve the migration of the SO_2 group in chemical reaction, and does not appear likely. Geometrically, however, all three structures are possible.



(XI.)



(XII.)



(XIII.)

The dimensions of the unit cell indicate that the molecule lies approximately along the *c* crystal axis, and the data are in general compatible with structure (XI). Comparison of the (*h*0*l*) series of reflections with those of the di-*p*-tolyl compound (described below) indicates that, although the crystals are isomorphous, there must be a certain shift in the molecular arrangement in passing from the phenyl to the tolyl compound. Because of this, the comparison is not of immediate assistance in elucidating the detailed structure, and it is necessary to deal with the compounds individually. Patterson and Harker projections have been made, but the large number of parameters (31) renders the interpretation difficult. Further work is in progress.

Bis-p-*tolylsulphonyl Trisulphide*, $C_{14}H_{14}O_4S_5$.—*Crystal data.* *M*, 406·4; m. p. 180°; *d*, calc. 1·528, found 1·547; tetragonal trapezohedral, $a = 7{\cdot}70 \pm 0{\cdot}02$, $c = 29{\cdot}50 \pm 0{\cdot}06$ A. Absent spectra, (*h*00) when *h* is odd, (0*k*0) when *k* is odd, (00*l*) except when $l = 4n$. Space-group, D_4^4–$P4_12_12_1$ (or D_4^8–$P4_32_12_1$). Four molecules per unit cell. Molecular symmetry, two-fold axis perpendicular to (110). Volume of the unit cell, 1749 A.^{3}. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$), $\mu = 60{\cdot}3$ per cm. Total number of electrons per unit cell = F(000) = 840.

The crystal habit is the same as that of the isomorphous diphenyl compounds (see Groth, *op. cit.*), and from the space-group data the same conclusions can be drawn regarding the possible molecular configurations (XI, XII, or XIII). The distribution of intensities in the (*h*0*l*) zone of reflections is, however, considerably different from that of the diphenyl compound. The additional methyl groups will affect the molecular orientation to some extent, and it is to be expected that the effect on the intensities will be more difficult to interpret than in a space-group of lower symmetry. As the dimensional change is confined almost entirely to a *c* axis expansion of 3·2 A. in the di-*p*-tolyl compound, it is clear that the long axis of the molecule must lie mainly in the direction of the *c* axis.

Conclusions.

A very interesting fact which emerges from this survey is that at least five, and possibly six out of the ten types of molecule examined display a two-fold axis of symmetry. No other element of molecular symmetry has been detected with certainty, although a centre of inversion is possible in the two disulphones. Further, the two-fold axis of symmetry is present in *all* the molecules which contain groups of three or more sulphur atoms. From this it is immediately clear that there is no possibility of side co-ordination to a single sulphur atom in either the tri- or the penta-sulphides or their sulphones. In all cases the balance of the evidence is in favour of extended zigzag sulphur chains, with other groups attached in approximately tetrahedral positions.

The difficult problem of detailed structure analysis for these complicated types of molecule has been simplified by this survey, and in particular by the dimensional comparisons between the phenyl and the tolyl compounds. It is now easy to select the more promising examples and form a preliminary estimate of the orientation of the molecule in the crystal lattice. In most cases, however, a large number of parameters remain to be determined. The assumption of a centre of symmetry in the triclinic disulphones is likely to be justified and will simplify the problem. In the monoclinic disulphonyl sulphides a preliminary orientation can be deduced from the outstanding intensities and by comparisons between the phenyl and the tolyl compounds. The higher crystal symmetry of the tetragonal disulphonyl trisulphides does not simplify the problem, although the main outlines of these structures can be predicted. In the trisulphides themselves, the iodine atoms in the di-iododiethyl compound (which very curiously belongs to the same space-group as the disulphonyl trisulphides) may be utilised to effect a fairly direct analysis of the atomic positions.

Experimental.

The *X*-ray measurements were in all cases carried out with Cu-*K*α radiation, $\lambda = 1{\cdot}54$ A., except for a few Laue photographs taken with white radiation and used to establish the symmetry of the tetragonal crystals. For axial-length measurements and space-group determinations, rotation, oscillation, and moving-film photographs were taken on small single-crystal specimens. Intensity surveys were carried out on layer line moving-film photographs, by visual estimates on calibrated films, employing the multiple film technique (Robertson, *J. Sci. Instr.*, 1943, **20**, 175). The absorption coefficient is high for many of the crystals described, and rough corrections were applied where necessary, but the factors were reduced as far as possible by careful selection or cutting of very small specimens (0·1—0·5 mm.) of nearly square cross-section normal to the rotation axis. Density determinations were made by flotation in suitable liquids.

Diphenyl disulphide was prepared by oxidation of thiophenol with ferric chloride (Zincke and Frohneberg, *Ber.*, 1910, **43**, 840). After recrystallisation from ethyl alcohol, long needles, m. p. 59°, suitable for *X*-ray examination were obtained.

Di-*p*-tolyl disulphide was prepared by oxidation of thio-*p*-cresol with ferric chloride or with iodine (*idem, ibid.*). Recrystallisation from ethyl alcohol gave long needles, m. p. 47°.

2 : 2′-*Di-iododiethyl trisulphide.* A pure specimen of this compound was supplied by C.D.E.S., Porton. Recrystallisation from alcohol–benzene yielded flat plates, m. p. 110°, from which sections suitable for *X*-ray examination were cut.

2 : 2′-*Dichlorodiethyl trisulphide.* This compound was also obtained from C.D.E.S., Porton. The low m. p. (27°) made crystallisation difficult. Benzene was found to be the most suitable solvent, and by slow cooling a few specimens suitable for *X*-ray examination were obtained.

Diphenyl disulphone was prepared by oxidation of benzenesulphinic acid with powdered potassium permanganate in cold glacial acetic acid (Hilditch, *J.*, 1908, **93**, 1526). Slow crystallisation from glacial acetic acid yielded small crystals, approximately rhombohedral, m. p. 193°.

Di-*p*-tolyl disulphone was prepared by interaction of *p*-toluenesulphonyl chloride and sodium *p*-toluenesulphinate in a mixture of ether and water (Kohler and MacDonald, *Amer. Chem. J.*, 1899, **22**, 222). Slow crystallisation from glacial acetic acid gave small thick prisms, m. p. 210° (decomp.).

Bisphenyl- and bis-*p*-tolyl-sulphonyl sulphide were prepared by treatment of the corresponding sodium sulphinates with sulphur dichloride in dry carbon tetrachloride (Troeger and Hornung, *J. pr. Chem.*, 1899, **60**, 113). Crystallisation from glacial acetic acid yielded lath-like crystals elongated along the *b* crystal axis, m. p. 133° for the phenyl and 138° for the *p*-tolyl compound.

Bisphenyl- and bis-*p*-tolyl-sulphonyl trisulphide were prepared by treatment of the corresponding sodium thiosulphonates with sulphur dichloride in dry carbon tetrachloride (Troeger and Hornung, *loc. cit.*). Crystallisation from glacial acetic acid yielded beautiful bipyramidal crystals, m. p. 102° for the phenyl and 180° for the *p*-tolyl compound.

We thank the Chief Scientist, Ministry of Supply, for permission to publish this paper, and one of us (A. McL. M.) is indebted to the Carnegie Trustees for a Scholarship which enabled him to take part in this work.

UNIVERSITY OF GLASGOW. [*Received, April 25th*, 1947.]

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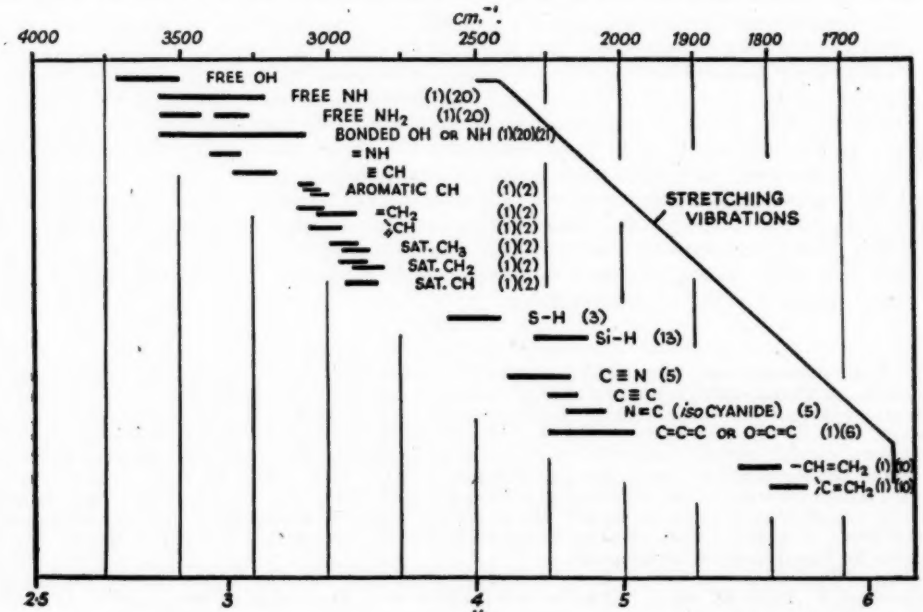
81. *The Correlation of Vibrational Absorption Spectra with Molecular Structure.*

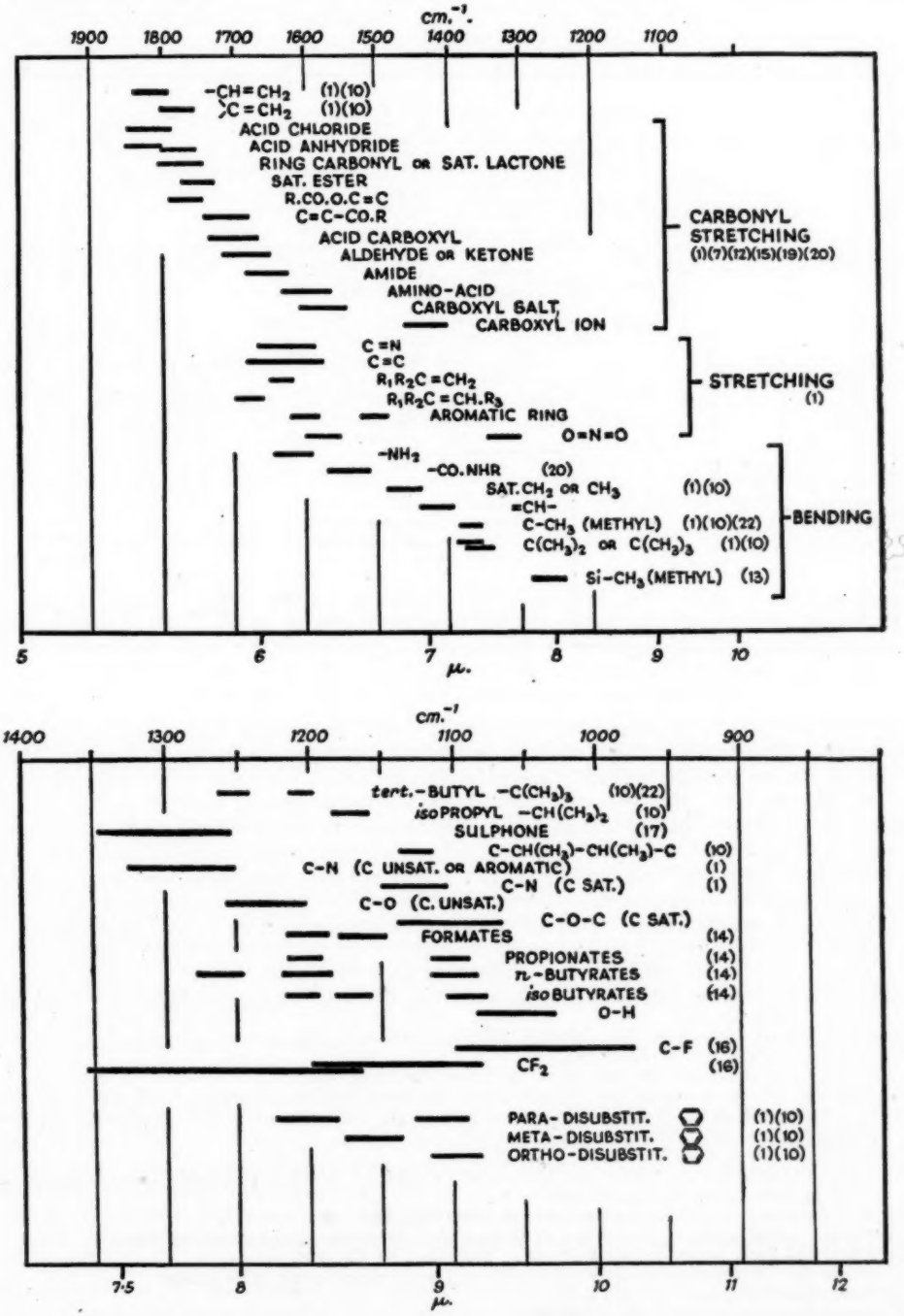
By H. W. THOMPSON.

Correlation rules are given relating vibrational spectra to characteristic groupings.

THE use of vibrational spectra for structural diagnosis is becoming increasingly important in the study of complex organic substances. The recent rapid developments of experimental technique have made it possible to compare the spectra of many related series of molecules, from which it has been found that certain groups have characteristic vibration frequencies



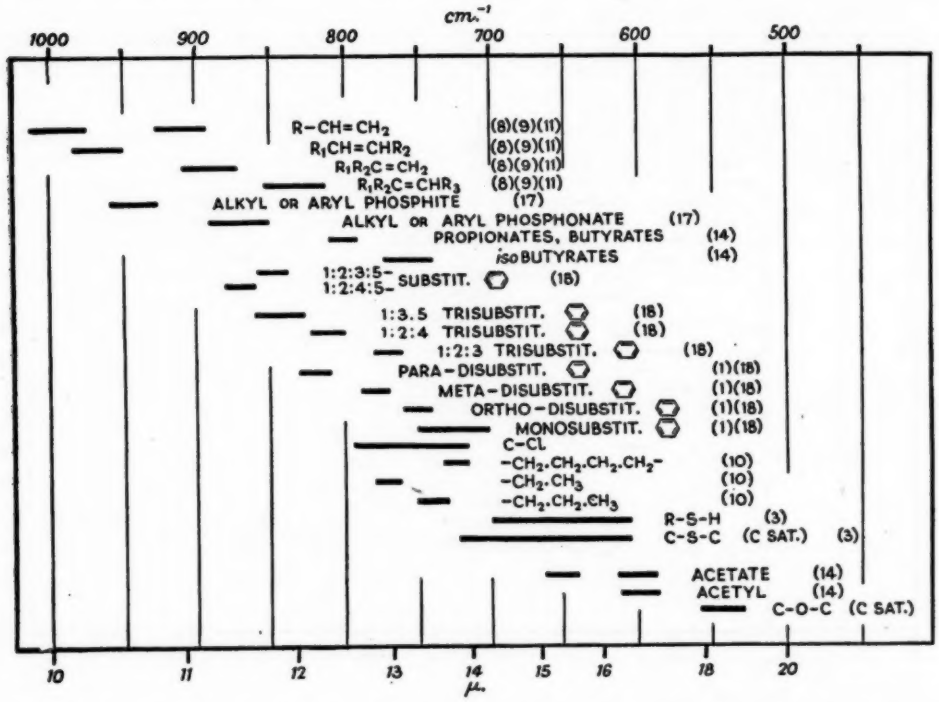
giving rise to marked absorption bands which persist in different compounds. Further, with some linkages or groups such as the carbonyl group, small specific alterations of the joining-



atoms or linkages lead to small but characteristic displacements of the vibration frequencies, and this occasionally provides a further refinement in the diagnosis.

Since it is at present impossible to publish curves for all the substances which have been

examined, some correlation rules have been drawn up in the Figures, many of which have been illustrated in recent papers. The charts have been drawn in a manner previously adopted by Barnes, Williams, and Gore, with whom the correlation rules have recently been discussed.



Most of the vibration frequencies given relate to fairly strong absorption bands which can be picked out in the spectrum unless there is accidental overlapping with other bands. Many of the rules given are not infallible, and special electronic effects may lead to abnormalities. The rules should, therefore, be taken as general guidance to be applied with proper caution. In addition, the state of aggregation in which a substance is measured may be of importance. References are given on the charts to some of the papers from which the rules have been drawn. The list is not complete, for some of the correlations are now sufficiently well known to make details superfluous. The rules may be helpful in designing a punched card index of the vibrational spectra of chemical compounds which is under consideration by several laboratories.

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THE PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, September 24th*, 1947.]

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82. *Bond Energies in Peroxides, and the Energy evolved in the Reaction* $H + O_2 = HO_2$.

By A. D. WALSH.

The bond energies in hydrogen peroxide, organic peroxides, and the radical HO_2 are considered. Many reasons are given why a recent estimate by Glockler and Matlack of the OO bond energy in hydrogen peroxide appears too low: the true value is considered to be ~ 64 kcals./mole, and the OO dissociation energy in the same molecule is ~ 56 kcals./mole. In organic peroxides the indications are that, other things being equal, the OO bond strength increases with increasing transfer of negative charge to the bond: an explanation of this in terms of increased "overlap" is offered. Various lines of evidence point to the fact that the energy evolved in the gas reaction $H + O_2 = HO_2$ is greater than has usually been supposed: a value ~ 60 kcals./mole or more seems more probable than one in the range 40—50 kcals./mole. In other words, HO_2 in its ground state is likely to be more inert than has previously been supposed.

THE vast importance of peroxides in many fields of chemistry is now recognised. Knowledge of their properties is still meagre in the extreme. The following notes attempt to add a little to the as yet rudimentary understanding of peroxide thermochemistry. They also consider the energy evolved in the reaction $H + O_2 = HO_2$. This reaction is of fundamental importance for the theory of the hydrogen–oxygen reaction and indeed of oxidations in general. Although the radical has frequently been invoked to explain reactions, there has been no commensurate consideration of its heat of formation, though a knowledge of this quantity is essential in deciding the probability of the postulated reactions. We begin by considering the bond strengths in the hydrogen peroxide molecule.

Bond Strengths in Hydrogen Peroxide.—Pauling ("Nature of the Chemical Bond", Cornell, 1940) assumed the OH bond strengths in water and hydrogen peroxide to be identical (110 kcals./mole): in consequence, from thermal data, he derived the value 35 kcals./mole for the OO bond energy in hydrogen peroxide. Skinner (*Trans. Faraday Soc.*, 1945, **41**, 645), on the basis of consideration of various resonance structures, decided that the OH bond was weaker in hydrogen peroxide than in water and consequently arrived at the value 52 kcals./mole for the OO bond energy. Glockler and Matlack (*J. Chem. Physics*, 1946, **14**, 504) have recently argued that Pauling's value is to be preferred to that of Skinner. Evidence is now cited that the true value is even higher than that of Skinner.

We shall use the term "bond energy" to mean an energy quantity characteristic of the bond as it actually exists in the equilibrium state of the molecule: it is chosen (Walsh, *Trans. Faraday Soc.*, 1947, **43**, 60; *J.*, in course of publication) in such a way that (*a*) the sum of the bond energies is equal to the heat of atomisation of the molecule with respect to those atomic states that correspond to the valencies of the atoms of the molecule, and (*b*) it serves as a parameter for the interconversion of such bond properties as force constant, length, ionisation potential, etc., standard points for the relation of bond energy to these properties being provided by molecules where all the bonds are the same. The peroxide bond energy in hydrogen peroxide will not be the same as the bond *dissociation energy*, since the OH bonds in the molecule are not identical with that in the free OH radical. Glockler and Matlack do not distinguish between bond and dissociation energy. Bichowsky and Rossini's data for the heat of formation of gaseous hydrogen peroxide being accepted, then, as Skinner showed, the heat of atomisation is 255·7 kcals. Since the dissociation energy of the OH radical is ~ 100 kcals. (Dwyer and Oldenberg, *J. Chem. Physics*, 1944, **12**, 351), the dissociation energy of the OO bond in hydrogen peroxide follows unambiguously as ~ 56 kcals.

In three papers (Walsh, *Trans. Faraday Soc.*, 1946, **42**, 56; 1947, **43**, 60, 158), it has been shown, mainly from a study of the ionisation potentials of non-bonding electrons, that the more polar a given bond the weaker it is, *i.e.*, the less its stretching force constant and bond energy and the greater its length. This fact means that the resonance description of bond polarity as due to ionic–covalent resonance is only helpful in assessing the bond energies in hydrogen peroxide if supplemented by discussion of the energies of stretching and compression of bonds (Walsh, *Ann. Reports*, in the press).

Since the oxygen atom in water has two hydrogen atoms on which to expend its electron attraction, whereas in the OH radical it has only one, we expect the electrons of the bond in the OH radical to be more polarised than those in the OH bond of the water molecule. The dipole in each bond of H_2O tends to reduce that in the other bond. Hence, if E and D signify bond and dissociation energy respectively,

$$D(\mathrm{H{-}OH})_{\mathrm{H_2O}} > E(\mathrm{O{-}H})_{\mathrm{H_2O}} > E(\mathrm{O{-}H})_{\mathrm{OH\ rad.}}$$

—an expectation fully confirmed by the facts: $D(\mathrm{H{-}OH})_{\mathrm{H_2O}} = 118$ kcals. (Dwyer and Oldenberg, *loc. cit.*), $E(\mathrm{O{-}H})_{\mathrm{OH\ rad.}} = 100$ kcals., and $E(\mathrm{O{-}H})_{\mathrm{H_2O}} = 110$ kcals. The weakness of the bond in the OH radical is shown further in its length (r) and stretching force constant (k): $r(\mathrm{OH})_{\mathrm{OH\ rad.}} = 0{\cdot}971$ A. (Herzberg, "Molecular Spectra and Molecular Structure", Prentice Hall, 1939), $r(\mathrm{OH})_{\mathrm{H_2O}} = 0{\cdot}955$ A. (*idem*, "Infra-red and Raman Spectra", Van Nostrand, 1945); $k(\mathrm{OH})_{\mathrm{OH\ rad.}} = 7{\cdot}12 \times 10^5$ dynes/cm., $k(\mathrm{OH})_{\mathrm{H_2O}} = 7{\cdot}66 \times 10^5$ dynes/cm. (*idem.*, 1945, *loc. cit.*).

Now the attachment of the electronegative (OH) group to the O atom of a hydroxyl group must make the bond in that hydroxyl group more polar; *i.e.*, the OH bond in the hydrogen peroxide molecule must be slightly more polar and therefore slightly weaker than the bond in the OH radical. Confirmation of this is to be seen in (*a*) the OH length reported by Giguère (quoted in *Chem. Abs.*, 1946, **40**, 1072) for hydrogen peroxide: $r(\mathrm{OH})_{\mathrm{H_2O_2}} = 1{\cdot}01 \pm 0{\cdot}03$ A., $r(\mathrm{OH})_{\mathrm{OH\ rad.}} = 0{\cdot}97$ A.; (*b*) the OH bond stretching force constant reported (Bailey and Gordon, *Trans. Faraday Soc.*, 1938, **34**, 1133) for hydrogen peroxide: $k(\mathrm{OH})_{\mathrm{H_2O_2}} = 6{\cdot}5 \times 10^5$ dynes/cm., $k(\mathrm{OH})_{\mathrm{OH\ rad.}} = 7{\cdot}1 \times 10^5$ dynes/cm. We therefore have strong grounds, from several different sources, for asserting that the OH bond energy in hydrogen peroxide must be a few kcals. *below* the strength in the OH radical (100 kcals./mole).

From the heat of atomisation, the expectation that $E(\mathrm{OH})_{\mathrm{H_2O_2}}$ must be less than 100 kcals. means a lower limit of 56 kcals. for $E(\mathrm{OO})_{\mathrm{H_2O_2}}$. If we choose a value ~ 96 kcals. for $E(\mathrm{OH})_{\mathrm{H_2O_2}}$, we obtain $\simeq 64$ kcals. for the OO bond energy in hydrogen peroxide. Some confirmation of this choice may be seen as follows:

(1) The expected sequence

$$E(\mathrm{Se{-}Se}) < E(\mathrm{S{-}S}) < E(\mathrm{O{-}O})$$

accords well with values for $E(\mathrm{O{-}O})$ in the range 56—70, since $E(\mathrm{Se{-}Se})_{\mathrm{Se_8}}$ is 41 kcals. and $E(\mathrm{S{-}S})_{\mathrm{S_8}}$ is 54 kcals. (Skinner, *loc. cit.*).

(2) Though the precise value for $E(\mathrm{O{-}O})$ will depend upon the particular peroxide in which the peroxide bond is situated, the variation will not be great. The value found by Bolland and Gee (*Trans. Faraday Soc.*, 1946, **42**, 244) for the OO dissociation energy of a hydroperoxide of type R·CH:CH·CH(O·OH)·R is 66 kcals., and the dissociation energy of the OO bond in persulphates is 57 kcals. (Palmer, "Valency", Cambridge, 1944). Since E is probably not far different from D in these compounds, these values may be said to support the range of our choice for $E(\mathrm{OO})_{\mathrm{H_2O_2}}$.

(3) Although elsewhere (Long and Walsh, *Trans. Faraday Soc.*, 1947, **43**, 342) we have criticised the over-rigid application of the empirical iso-electronic principle, it is a well-known fact in valency theory that a group XH often has properties close to those of the "compound atom". We therefore expect a similarity between the fluorine and hydrogen peroxide molecules. The fluorine molecule has a bond length of 1·45 A. and a bond energy at room temperature of 63·5 kcals. (Skinner, *loc. cit.*). The Raman spectrum of fluorine has not been measured and, in consequence, the force constant of the molecule is not known directly, but it may be estimated by extrapolating a graph of force constant against bond energy for the halogen molecules I_2, Br_2, Cl_2. Such a graph yields a value $3{\cdot}6 \times 10^5$ dynes/cm. for the fluorine force constant. The stretching force constant reported (Bailey and Gordon, *loc. cit.*) for the OO bond in hydrogen peroxide is also $3{\cdot}6 \times 10^5$ dynes/cm. [which value receives some confirmation since, *via* Badger's rule, it gives $r(\mathrm{OO})$ as 1·48 A., in good accord with the electron-diffraction value (Giguère and Schomaker, *J. Amer. Chem. Soc.*, 1943, **65**, 2025)]. Since k and r appear to be so closely similar

for the FF and $OO_{H_2O_2}$ bonds, we expect close similarity of E, in full agreement with our choice for $E(OO)_{H_2O_2}$.

Badger's rule (Garner and Yost, *J. Amer. Chem. Soc.*, 1937, **59**, 2738) yields a value 836 cm.$^{-1}$ for the fundamental frequency of F_2. This corresponds to $k \sim 4 \times 10^5$ dynes/cm. Gale and Monk (*Astrophys. J.*, 1924, **59**, 125; 1929, **69**, 77) have assigned the value 1130 cm.$^{-1}$ to this frequency. This corresponds to $k \sim 7{\cdot}1 \times 10^5$ dynes/cm. Gordy (*J. Chem. Physics*, 1946, **14**, 305), from an empirical relation involving bond length, has predicted $k(F_2)$ as $7{\cdot}93 \times 10^5$ dynes/cm. A value of this magnitude is obtained from a plot of force constant against bond length for I_2, Br_2, and Cl_2. The evidence against these high values includes: (*a*) they do not accord with Badger's rule; (*b*) Gordy's relation fails for the hydrogen molecule—it is not unlikely therefore that it fails also for the fluorine molecule; (*c*) they conflict with the similarity of iso-electronic molecules stressed here; (*d*) Gaydon (" Dissociation Energies," Chapman and Hall, 1947) has recently inclined to the view that $D(F_2)$ is rather less than 63·5 kcals.: while this may affect the argument of similarity between F_2 and H_2O_2, it certainly renders high values for $k(F_2)$ still less likely.

Continuing the sequence from F_2 to $(HO)_2$ to $(H_2N)_2$, we find the NN bond in hydrazine to have closely similar characteristics to the FF and peroxide bonds. It is known to have a bond length of 1·47 A. and a stretching force constant of $3{\cdot}6 \times 10^5$ dynes/cm. (Branch and Calvin, " Theory of Organic Chemistry ", Prentice Hall, 1941). One may predict the NN bond energy in hydrazine to be close to 64 kcals., though the dissociation energy will probably be considerably lower, as it is in hydrogen peroxide. Table II shows the similarity between the H_2N–NH_2, HO–OH and F–F bonds. We should not expect the similarity to extend to the CC bond of ethane, since it is known that in ethane hybridisation of the 2*s* and 2*p* atomic wave functions becomes more important. The presence of *s* character in the carbon valencies makes the CC bond appreciably stronger than the NN, OO, or FF bonds (Walsh, in course of publication).

TABLE I.

Comparison of the halogens.

	k, 10^5 dynes/cm.	r, A.	E (room temp.), kcals./mole.		k, 10^5 dynes/cm.	r, A.	E (room temp.), kcals./mole.
I_2	1·72	2·667	36·4	Cl_2	3·29	1·989	58·1
Br_2	2·46	2·284	46·3	F_2	3·6 (est.)	1·45	63·5

TABLE II.

Comparison of N_2H_4, H_2O_2, *and* F_2.

	k, 10^5 dynes/cm.	r, A.	E, kcals./mole.
H_2N–NH_2	3·6	1·47	—
HO–OH	3·6	1·47	64
F–F	3·6 (est.)	1·45	64

There is thus a considerable body of concordant evidence against a value of 35 kcals. for $E(OO)_{H_2O_2}$ and in favour of $\sim$ 64 kcals. This must mean that the graph plotted by Glockler and Matlack, namely, of dissociation energy against r for different states of the O_2 molecule (built up from O atoms in different atomic states), is not a valid way of estimating the bond energy in hydrogen peroxide. It has to be emphasised in this connection that a smooth curve of E–r is only to be expected for bond energies as distinct from dissociation energies. These are not necessarily identical even for diatomic molecules. For example, as Mulliken (*J. Chem. Physics*, 1939, **7**, 28) has shown, the N→V character of the Schumann–Runge bands of O_2 and the ionic nature (in A.O. approximation) of the V state show that the $^3\Sigma_u^-$ state of O_2 must be considered as built, at least partly, from $O^+ {}^4S + O^- {}^2P$—although the state dissociates into $O {}^3P + O {}^1D$. Penney (" Quantum Theory of Valency ", Methuen, 1935) has described how the " valency state " of an atom in a molecule is not equivalent to its ground state; while Heitler (" Wave Mechanics ", Oxford, 1945) has emphasised the interaction of potential energy curves as a result of the operation of the " non-crossing rule ". It is clear that the dissociation energy of a molecule is not necessarily a quantity directly related to properties, such as force constant and inter-nuclear distance, characteristic of the equilbrium state of the molecule.

Finally, we may observe that the weakness of the OO bond (cf. the BH bond; Walsh, *J.*, 1947, 89) means that the orbital concerned in it has a large spatial spread. This is likely to prove a significant point in the understanding of peroxide chemistry; *e.g.*, it partly accounts

for the formation of complexes in which the peroxide bond has attached to it an atom of acceptor properties such as a ferrous ion.

Bond Strengths in Other Peroxides.—The author has pointed out (*Trans. Faraday Soc.*, 1946, **42**, 264) that the variations in OO bond strength from molecule to molecule can partly be understood in terms of charge transfer effects established by the study of the ionisation potentials of non-bonding electrons in alkyl halides. The greater the negative charge transfer to the OO group, frequently the greater the OO bond strength. The OO strength should according to this view increase in the order H–OO–H, Me–OO–H, Et–OO–H, Pr^{β}–OO–H, Bu^{γ}–OO–H, while the corresponding dialkyl peroxides should be still more stable—though there may be offsetting factors, as discussed below. Milas and Surgenor (*J. Amer. Chem. Soc.*, 1946, **68**, 205) have confirmed the remarkable stability of di-*tert.*-butyl peroxide.* Berezovskaja, Varfolomeeva, and Stefanovskaja (*J. Physical Chem. Russia*, 1944, **18**, 321) have adopted a conclusion closely similar to ours, namely, that the stability of organic peroxides increases with the number of carbon atoms in the radicals attached to the OO group.

The trend of the peroxide bond strengths can be seen by considering the reaction

$$R{\cdot}O{\cdot}OR' \longrightarrow R{\cdot}OR' + O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and using the heats of peroxide formation found by Stathis and Egerton (*Trans. Faraday Soc.*, 1940, **36**, 606). Assuming the CO and OH bonds and the internal bonds of the alkyl radicals to have the same strength in the peroxide as in the alcohol or ether, the heat absorbed by (1) readily gives the peroxide bond energy. For Et·O·OH, Pr·O·OH, and Et·O·OEt, the values come to 51, 54, and 62 kcals./mole, respectively. It is the trend only of these figures that is important. The absolute values must be low because, owing to polarity effects, (*a*) the CO bond will actually be weaker in R·O·OH than in R·OH, and (*b*) the OH bond will actually be weaker in R·O·OH than in R·OH—so that the energy absorbed by (1) is actually lower than E(OO). We therefore conclude that our value $\approx$ 64 kcals./mole for E(OO) in hydrogen peroxide is not inconsistent with the thermal data of Stathis and Egerton for the above three compounds and with the idea of increasing OO strength with increasing charge transfer.

According to the figure given by Kassatochkin (*Compt. rend. Acad. Sci. U.S.S.R.*, 1945, **47**, 193), from *X*-ray work, the bond length in the ion $^{-}O{-}O^{-}$ is only 1·35 A. as against 1·47 A. given by electron diffraction (Giguère and Schomaker, *loc. cit.*) (and by *X*-ray work in the case of the compound of urea with hydrogen peroxide; Lu, Hughes, and Giguère, *J. Amer. Chem. Soc.*, 1941, **63**, 1507) for the OO bond length in hydrogen peroxide; indicating a stronger bond in O_2^{--} than in hydrogen peroxide, in spite of the adjacent similar charges in O_2^{--}.

One may ask the reason for the increase of OO bond strength with increasing negative charge transfer to the bond. Up to a point, increasing the electronegativities of the atoms at the ends of a bond increases the bond strength [*e.g.*, E(II) < E(BrBr) < E(ClCl) < E(FF), and E(SeSe) < E(SS) < E(OO) as shown above]; but it is clear that this increase of electronegativity as a means of increasing bond strength can go too far (cf. Walsh, *J. Chem. Physics*, 1947, **15**, 688): after a certain point it will weaken the bond because the atomic orbitals that have to overlap to give the bond become so small that strong overlap cannot occur because it would involve the nuclei being so close as to repel each other strongly. In such cases (which will only occur in bonds between atoms of high electronegativity) *decrease* of electronegativity of the bonded atoms will strengthen the bond. An example is the way the bond in F_2 strengthens if one of the F atoms is replaced by Cl to give FCl—in spite of the fact that the bond in FCl is polar. The peroxide bond apparently affords another example of this reduced overlap effect.

Rieche ("Alkylperoxyde und Ozonide," Steinkopf, Dresden, 1931, p. 128) suggests that the dipole moment of peroxides decreases in the sequence from hydrogen peroxide *via* alkyl hydroperoxides to dialkyl peroxides. Chromatographic analysis of peroxide mixtures (Eggersglüss, unpublished work) fully substantiates this. The greater dipole moment in alkyl hydroperoxides relative to dialkyl peroxides is one of the factors causing the former to have much higher boiling points than the latter. Thus the b. p. of $CH_3{\cdot}O{\cdot}OH$ is $\sim$ 40° at 65 mm., but that of $CH_3{\cdot}O{\cdot}OCH_3$ is only 13·5° at 740 mm., while that of *tert.*-butyl hydroperoxide is 33° at 17 mm., as against only 12—13° at 20 mm. for di-*tert.*-butyl peroxide. (Another, related, factor is of course the possibility of hydrogen bond formation in alkyl hydroperoxides.) At first sight this statement concerning the dipole moments appears to conflict with the statement that there is greater negative charge transfer to the OO group in a dialkyl than in an alkyl than in hydrogen

* Milas and Surgenor (*loc. cit.*, and *J. Amer. Chem. Soc.*, 1946, **68**, 643) and Milas and Perry (*ibid.*, p. 1938) have also confirmed the rules given by George and Walsh (*Trans. Faraday Soc.*, 1946, **42**, 94) for the decomposition of *tert.*-alkyl peroxides.

peroxide. Models of dialkyl peroxides, however, soon show that, whereas in hydrogen peroxide the angle between the planes containing the OH bonds is $\sim 100°$ (Penney and Sutherland, *Trans. Faraday Soc.*, 1934, **30**, 898; *J. Chem. Physics*, 1934, **2**, 492), the angle between the corresponding planes in dialkyl peroxides must be close to 180°. This is particularly so in di-*tert.*-butyl peroxide which must conform very closely to a *trans*-molecule. Hence, whereas in the hydrogen peroxide molecule the two OH dipoles only partly oppose each other, in dialkyl peroxides the corresponding dipoles must be in much greater opposition. Alkyl hydroperoxides, as a result of these steric effects, must occupy an intermediate position.

The reason for the skew nature of the hydrogen peroxide molecule is the repulsion of the charge clouds of the lone-pair electrons on the oxygen atoms: if these charge clouds were arranged with their axes parallel, the OO bond would be weakened, it is estimated, by some 10 kcals. (Penney and Sutherland, *loc. cit.*). In a peroxide such as di-*tert.*-butyl peroxide, therefore, it has to be remembered that, although the magnitude of the negative charge transfer to the OO group is a factor that probably tends strongly to increase the OO strength, on the other hand the *trans*-arrangement of the molecule will mean a weakening of OO strength by some 10 kcals. We may further observe that the smallness of the over-all dipole moment in di-*tert.*-butyl peroxide, relative to that of hydrogen peroxide, must be an important factor causing the chemical inertness of the molecule.

The above serves to emphasize that charge transfer can only be one of many factors affecting OO bond strengths. It should also be remembered that the partial correlation is with bond energies and not necessarily with *dissociation* energies. Further, although it can be shown that the reaction

$$CH_3{\cdot}CH_2{\cdot}O{\cdot}OH_{vap.} = CH_3 + H{\cdot}CHO + OH$$

absorbs 66·9 kcals. (Walsh, *Trans. Faraday Soc.*, 1947, **43**, 297), and though little or none of this energy is expected to be absorbed in the split

$$CH_3{\cdot}CH_2{\cdot}O = CH_3 + H{\cdot}CHO$$

[which breaks a CC bond (requiring $\gtrsim$ 80 kcals.: cf. Skinner, *Nature*, 1946, **158**, 592), forms a $>C{=}O$ from a $>C{-}O^-$ (evolving $\gtrsim$ 190—90 kcals.: cf. Skinner, 1946, *loc. cit.*, with Walsh, *Trans. Faraday Soc.*, 1947, **43**, 60) and makes minor changes in CH strengths], the energy of activation of gas-phase peroxide decompositions lies near the range 30—40 kcals. (*e.g.*, Harris and Egerton, *Proc. Roy. Soc.*, 1938, *A*, **168**, 1). This means that the energy of activation apparently does not (as has sometimes been supposed) concern simply the fission of the OO bond and must be interpreted with great caution. In a probably similar way, nitrate and nitrite decompositions (Phillips, *Nature*, 1947, **160**, 753; Rice and Radowskas, *J. Amer. Chem. Soc.*, 1935, **57**, 350) have apparent activation energies near the range 30—40 kcals., although E(O–N) is probably considerably higher. [Thus, D(O–N) in HNO_3 can be shown to be $\sim$ 54 kcals.: cf. Skinner, 1945, *loc. cit.*] *

The Energy Evolved in the Reaction $H + O_2 = HO_2$.—A knowledge of the heat of the reaction

$$H + O_2 = HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

is essential for progress to be made in deciding the most probable reaction schemes governing the combustion of hydrogen and hydrocarbons.

Past estimates. Bodenstein and Schenk (*Z. physikal. Chem.*, 1933, *B*, **20**, 420), from a study of the inhibition by oxygen of the hydrogen–chlorine reaction, estimated the heat of reaction (2) to be about 40 kcals. Haber and Weiss (*Proc. Roy. Soc.*, 1934, *A*, **147**, 350), from consideration of the ferrous ion–hydrogen peroxide system, estimated a value $\sim$ 50 kcals. Bray (*J. Amer. Chem. Soc.*, 1938, **60**, 82) estimated 51 kcals. on the basis of several assumptions, including that of the ionisation constant of HO_2 being the same as that of HOCl. Others have used values varying between 40 and 50 kcals.

Bodenstein's estimate depends upon a particular set of reactions being assumed for the H_2–Cl_2–O_2 system. This set is by no means unique, and little reliance can be put upon the upper limit of 44 kcals. given by Bodenstein. Haber and Weiss's estimate depends upon several assumptions (*e.g.*, they assume a value for the experimentally unknown velocity constant of the reaction $Fe^{++} + HO_2 \longrightarrow Fe^{+++} + HO_2^-$). Also, their estimate, like that of Bray, is for

* The reduced overlap effect consequent upon too high an electro-negativity product should be less important for O–N than for O–O bonds. Also the high dipole of a NO_2 group causes a polarity in the ON bond of nitrates which is greater the greater the charge transfer from the alkyl groups to the O atom. For these and other reasons, it is not surprising that the order of stability to dissociation of ON bonds in alkyl nitrates is Me>Et>*n*-Pr(Phillips, *loc. cit.*).

reaction in solution. One can hardly conclude that the evidence for the energy evolved by (2) in the gas phase lying in the range 40—50 kcals. is at all strong. We propose in what follows to give several lines of evidence which suggest a value in the range 60—70 kcals.

Evidence from the electronic structure of O_2. Haber and Weiss (*loc. cit.*), estimating the energy of (2) to be 50 kcals., remarked " The great difference between this value and the much larger value for

$$H + HO_2 = H_2O_2 \quad . . . . . (3)$$

is due to the fact that the double bond in the oxygen molecule must be opened to produce the first product, HO_2, but is already open for the second step to proceed ". This appears to be based upon an inadequate conception of the oxygen molecule. The paramagnetism of oxygen forces one to assume the existence of unpaired electrons in the molecule and therefore to abandon any close parallel between the bonding in the oxygen molecule and in the CC bond of ethylene. If we take an x axis along the OO bond, then one oxygen atom has a $2p_y$ odd electron and a $2p_z$ lone pair, while the other has a $2p_z$ odd electron and a $2p_y$ lone pair. Now the bonding that results from the interaction of an odd electron with an appropriate lone pair on an adjacent atom is considerable. For example, the first ionisation potential of a Cl_2 molecule corresponds to the removal of one of the non-bonding electons : that is, in Cl_2^+ one of the Cl atoms has an odd $2p_y$ electron, while the other has a $2p_y$ lone pair. Accordingly, we find the Cl–Cl bond to be appreciably stronger in Cl_2^+ than in Cl_2, as shown by the vibrational frequency and internuclear distance. This may in part be due to removal, in Cl_2^+, of some of the repulsion between two fully occupied p orbitals such as operates to make the hydrogen peroxide molecule skew, but the magnitude of the effect indicates an appreciable bonding due to the interaction of the odd $2p_y$ electron with the $2p_y$ lone pair.* Herzberg (1939, *op. cit.*) estimates $D(Cl_2^+)$ to be 4·4 v. (101 kcals.), while $D(Cl_2)$ is only 2·48 v. (57 kcals.). By analogy with the Penney–Sutherland treatment of hydrogen peroxide, the repulsion of two fully occupied p orbitals is hardly likely to account for much more than 10 kcals. of the difference. Pauling (" Nature of the Chemical Bond ", 1940) calls the interaction of an odd electron and a lone pair a " three electron bond " and finds evidence for such bonds being about half the strength of the corresponding normal electron-pair bonds. In this language the actual bond may be said to be a resonance hybrid of the two forms

$$\dot{A}\quad \dot{B}\!:\qquad :\!\dot{A}\quad \dot{B}$$
$$(a.)\qquad\qquad (b.)$$

or the actual wave function of the system may be written neither as ψ (a) nor as ψ (b) but as $a\psi(a) + b\psi(b)$. In molecular orbital language, of the three electrons concerned, two go into a bonding orbital of form $A\psi(A) + B\psi(B)$ and one into an anti-bonding orbital of form $A\psi(A) - B\psi(B)$. This means a net bonding effect contributed by two electrons minus one electron, that is, a bonding roughly half that prevailing in a normal electron-pair bond—in agreement with Pauling's conclusion. In this sense the so-called " three-electron " bond might be called a " one-electron " bond.

The much greater strength of the OO bond in O_2 (118 kcals.) than in H_2O_2 (64 kcals. according to our estimate above) is to be attributed to the existence of two " three-electron " bonds in O_2. Each " three-electron " bond is about half the strength of an ordinary O–O single bond $[\frac{1}{2}(118 - 64) = 27]$—a deduction which appears to confirm the approximate correctness of our estimate of the OO strength in H_2O_2, though we shall consider the matter in more detail below.

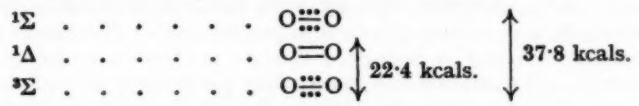
The two " three-electron " bonds in the O_2 molecule lie in planes at right angles and, to a first approximation, breaking the first (by addition of H to give HO_2) might be supposed not to disturb the second. Since the reaction

$$H + O_2 + H = H{\cdot}O{\cdot}OH \quad . . . . . (4)$$

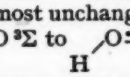
is known to liberate 138 kcals. (see the heat of atomisation of hydrogen peroxide quoted above), we might expect (2) to liberate 69 kcals. This figure has indeed been used by earlier authors (*e.g.*, Frankenburger and Klinkhardt, *Trans. Faraday Soc.*, 1931, **27**, 431; Dawsey, Urey, and Rice, *J. Amer. Chem. Soc.*, 1929, **51**, 1371), but the separation of (4) into two thermally equal steps has not previously been justified. We have, however, neglected certain points which it is necessary to consider in order to give the best estimate for the heat evolved by (2).

* In molecular-obitatal language, of course, the greater strength of Cl_2^+ than of Cl_2 is due to the removal of an electron from an anti-bonding orbital.

In the first place we have neglected the stabilising interaction of the two " three-electron " bonds in the oxygen molecule (Wheland, *Trans. Faraday Soc.*, 1937, **33**, 1499). Pauling (*op. cit.*, p. 253) gives the low-lying electronic states of the oxygen molecule as



The interaction of the two " three-electron " bonds may be either stabilising or repulsive: the $^1\Sigma$ state corresponds to the latter and the $^3\Sigma$ (or ground) state to the former. From the difference in the energies of the $^1\Sigma$ and $^3\Sigma$ states, the stabilising interaction of the two " three-electron " bonds in the ground state may be given as 18·9 kcals. The energy of the σ bond is expected to be not far from its value in hydrogen peroxide (cf. the usually assumed rough constancy of σ CC bonds): in both O_2 and H_2O_2 the charge clouds of the lone-pair electrons are oriented so as not to cause repulsion. Since the ground-state bond energy is 118 kcals., we may therefore estimate the energy of each " three-electron " bond as $\sim \frac{1}{2}(118 - 19 - 64) = 17{\cdot}5$ kcals. In the second place, the molecular-orbital description of the " three-electron " bond shows clearly that in this case it is not so much the σ bond that should be twice the strength of the " three-electron " bond, but a π bond between the nuclei In the $^1\Delta$ state there are no unpaired electrons and the bonding is somewhat analogous to that in ethylene. In this state, the bond energy is 118 − 22·4 kcals. Hence the energy of the second (or π) bond in this state must be about 118 − 22 − 64 = 32 kcals., and we note that the energy of each " three-electron " bond *is* roughly half this.

As compared with water, the two OH bonds in H_2O_2 are separated by an extra atom and also lie in different planes: removal of one H from H_2O_2 (unlike the case with H_2O) will leave the other OH bond almost unchanged; that is, $E(OH)_{H_2O_2} = E(OH)_{HO_2}$ to a good approximation. On passing from O⋮⋮O $^3\Sigma$ to  O=O, we break a " three-electron " bond (~ 17·5 kcals.), remove the stabilising interaction of the two " three-electron " bonds (~ 19 kcals.), and liberate an energy in forming the OH bond that must be close to that of $E(OH)_{H_2O_2}$ (*i.e.*, 96 kcals.). The net liberation of heat is thus 96 − (17·5 + 19) ≈ 60 kcals.

It is true that this calculation still neglects certain subsidiary effects—such as the change in strength of the second " three-electron " bond consequent upon the slight moving apart of the nuclei on breaking the first " three-electron " bond; the change in strength of the σ bond from HOOH to HO_2 to O_2; and the effect of the polarity of the OH bond in HO_2 on the OO strength (cf. the change in OO strength with charge transfer discussed earlier) but, in view of the uncertainty of the figures, the agreement with the figure required by other lines of evidence (see below) is not unsatisfactory. It is, however, just worth considering what effect on the result would come from taking a different value for the OO strength in H_2O_2. Using a figure lower by x for $E(OO)_{H_2O_2}$, we obtain $17{\cdot}5 + x/2$ for the energy of each " three-electron " bond and $96 + x/2$ for the energy of the OH bond in H_2O_2, so that the calculation of heat liberation is actually independent of x. On the other hand, as x increases, the strength of the " three-electron " bond becomes appreciably more than half that of the π bond in the $^1\Delta$ state.

It is also worth considering what would be the effect on the result if the energies of bonds involving O atoms were taken as related to a " valency state " of O y kcals. above the ground state. The high value of the O_2 force constant as compared with those of other bonds of known energy affords some justification for taking $E(O_2)$ as greater than $D(O_2)$, in order to preserve the utility of the concept of bond energy as a parameter related to bond force constants, irrespective of the nuclei concerned. Similarly, the force constants of OH bonds indicate bond energies greater than those obtained from heats of atomisation relating to oxygen atoms in the ^3P state. $E(O_2)$ then becomes $118 + 2y$ kcals. and $E(OH)_{H_2O_2}$ becomes $96 + y$ kcals. Hence $E(OO)_{H_2O_2}$ remains at 64 kcals. The energy of the " three-electron " bond in O_2 becomes $17{\cdot}5 + y$ kcals. Therefore, the energy evolved by (2) becomes $96 + y - (17{\cdot}5 + y + 19)$; *i.e.*, it remains unchanged at ~ 60 kcals.

Taking $E(OH)_{HO_2}$ as 96 means that an estimate of 45 kcals. for the energy liberated by (2) implies an OO bond strength in HO_2 of only 67 kcals. This is hardly compatible with the magnitude of the interaction that we expect to occur between the $2p_z$ odd electron and the $2p_z$ lone pair. An estimate of 60 kcals. for the energy liberated by (2) corresponds to an OO bond strength in HO_2 of 82 kcals./mole. It further corresponds to an energy liberated in (3) of 78 kcals.

So far, we have spoken mainly in terms of atomic orbital or pair-bond theory. On the molecular orbital theory, the oxygen molecule possesses (only orbitals built from $2p$ atomic orbitals being considered) six electrons in bonding orbitals and one electron in each of two anti-bonding orbitals. On passing from O_2 to HO_2, the OO strength weakens because the extra electron provided by the H atom passes partly into one of the OO anti-bonding orbitals. The structure approaches that obtained by fusing the H and one of the O nuclei, namely FO. The effect, in terms of energy, of an anti-bonding electron in O_2 is roughly given by $E(O_2^+) - E(O_2)$, *i.e.*, by 6·48 − 5·08 v. = 1·40 v. = 32 kcals. Hence, if formation of O–H liberates ~ 96 kcals., the energy evolved by (2) = 64 kcals. This is likely to be a minimum value since two of the OO anti-bonding electrons in HO_2 are now spending part of their time, not in the OO, but in the OH bond.

Evidence from interatomic distances of O_2, O_2^-, *and* O_2^{--}. Kassatochkin (*loc. cit.*) lists the following interatomic distances based on *X*-ray work:

O_2 1·20 A. O_2^- 1·27 A. O_2^{--} 1·35 A.

These distances support the thesis that the OO bond weakens roughly as much in going from O_2 to O_2^- as from O_2^- to O_2^{--}; and therefore by implication that, to a first, crude, approximation, destruction of one " three-electron " bond in the oxygen molecule leaves the other unaffected. Kassatochkin calculates $D(O_2^-)$ as 3·82 v. (88 kcals.), although the result is somewhat uncertain since it depends upon a value for the electron affinity of an oxygen atom (which he takes as 2·2 v. or 51 kcals.) and assumes the lattice energies of KCl and KO_2 to be the same. It is of interest, however, to note that his result, compared with $D(O_2) = 5{\cdot}09$ v., means a decrease in OO strength of 1·27 v. or 29 kcals./mole, in good agreement with our figure of 32 kcals. above, in passing from O_2 to O_2^-. The extra repulsion of parallel lone-pair charge clouds that must occur in O_2^- being neglected, (2) should liberate 96 − 29 = 67 kcals. Inclusion of the charge-cloud repulsion will raise this estimate, but not by much, since, in any case, owing to the polarity of the OH bond in HO_2, the condition of the OO group in HO_2 cannot be very different from that in the O_2^- ion. A value for the electron affinity of an oxygen atom higher by x kcals. would reduce the calculated energy in (2) by x.

Kinetic evidence from the H_2–O_2–NO_2 *system.* The kinetics of the thermal and photochemical H_2–O_2–NO_2 systems at temperatures above 300° are so similar that there can be little doubt that the NO_2 acts in the same way in both systems (Norrish and Griffiths, *Proc. Roy. Soc.*, 1933, *A*, **139**, 147). Since in the photochemical system NO_2 is known to act by decomposition to NO + O, the conclusion is that in the thermal system NO_2 is also dissociated to NO + O. This decomposition requires 71·5 kcals./mole (Gaydon, 1947, *loc. cit.*; the value 73 kcals. results from figures given by Biochwsky and Rossini, " Thermochemistry ", Reinhold, 1936). Dainton and Norrish (*Proc. Roy. Soc.*, 1941, *A*, **177**, 393) found evidence that NO_2 molecules were dissociated on collision with energy-rich links in the oxidation chains. The only plausible suggestion as to the nature of the " hot " links is—as Dainton and Norrish supposed—that they are HO_2 molecules carrying their energy of formation from H + O_2. Since an activation energy of 15 kcals. was found for the reaction whereby NO_2 is dissociated, we must have

$$15 + \text{energy evolved in (2)} \geqq 71{\cdot}5$$

or

$$\text{energy evolved in (2)} \geqq 56{\cdot}5 \text{ kcals.}$$

Evidence from HBr–O_2 *systems.* The sensitisation by O_2 of HBr additions to olefins at room temperature and of hydrocarbon oxidation by HBr [Vaughan and Rust, U.S.PP. (1946) 2,395,523; 2,403,722; 2,403,771] at temperatures around 150° is probably due to the formation of Br atoms by the reaction

$$HBr + O_2 = HO_2 + Br$$

Now $D(HBr) = 83$ kcals./mole (Herzberg, 1939, *loc. cit.*). Hence if (2) only liberates 45 kcals., an energy of activation (E_A) of at least 38 kcals. is needed. A reaction with such an E_A is not likely to be appreciable at temperatures as low as those at which the above-mentioned sensitisations occur. If, however, (2) liberates, say, 60 kcals., an E_A of only 23 or more is needed, which is more plausible for the observed temperature range of reaction.

[Since $D(HCl) = 103$ kcals. (Herzberg, 1939, *loc. cit.*), hydrogen chloride is only likely to bring about similar sensitisation at high temperatures. Norrish and Foord (*Proc. Roy. Soc.*, 1936, *A*, **157**, 503) find that it sensitises the oxidation of methane in the temperature range 600—700°.]

Conclusion.—Although it is not at present possible to arrive at a precise estimate of the

energy evolved in the gas phase by the reaction $H + O_2 = HO_2$, the cumulative effect of the above lines of evidence is to suggest that past estimates in the range 40—50 kcals. are too low. Until more precise evidence is forthcoming, it seems more accurate to take a value in the range 60—70 kcals. While this change may not seem very great, it is in fact of considerable significance for the reaction schemes postulated to represent the combustion of hydrogen and hydrocarbons.

HO_2 is inert for much the same reason as the O_2 molecule (in spite of its containing two unpaired electrons) is inert compared with many atoms or radicals: its odd electron is concerned in an attractive interaction with a parallel lone pair. Its inertness is shown, for example, in the inhibition by O_2 of the H_2–Cl_2 reaction and is reflected in the large energy evolved by reaction (2). In the same way the isoelectronic Cl_2^+ molecule has a high bond strength.

We conclude by considering very briefly the relevance of our discussion of the "three-electron" bonds in the oxygen molecule to the formation of organic peroxides from hydrocarbons.

Formation of Organic Peroxides from Hydrocarbons.—There is at present (see Symposium on Oxidation, *Trans. Faraday Soc.*, 1946, **42**, 99—398) unanimity of opinion that organic peroxides are formed from hydrocarbons during oxidation by the chains

$$R + O_2 = R{\cdot}O{\cdot}O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$R{\cdot}O{\cdot}O + RH = R{\cdot}O{\cdot}OH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where R is a hydrocarbon radical. There has been, however, only one careful consideration of the thermochemistry of these reactions, namely, that by Bolland and Gee (*Trans. Faraday Soc.*, 1946, **42**, 244). The energy liberated by (5) is mainly given by the expression

Energy liberated in forming R–O	—	Energy absorbed in breaking a three-electron bond	—	Energy of interaction of two three-electron bonds	—	Resonance energy of radical R
(X)		(Y)		(Z)		(R)

X will be slightly less than its value in methyl alcohol (90 kcals.: Skinner, *Nature*, 1946, **158**, 592) since the bond is expected to be more polar and therefore slightly weaker in a peroxide radical: a rough value might be 85 kcals. as a minimum. The energy liberated is therefore $\simeq 85 - (17{\cdot}5 + 19) - R$ or $48 - R$ kcals.

Reaction (6) liberates the energy of an OH bond (~ 98: slightly greater than in H_2O_2 because of charge transfer from R to the OO group) plus the resonance energy of the hydrocarbon radical formed (R) minus the energy of a CH bond (~ 100 kcals.) minus the energy of a three-electron bond ($\sim 17{\cdot}5$). Hence the energy liberated is $\simeq 98 - 100 - 17{\cdot}5 + R$ or $\simeq R - 19{\cdot}5$ kcals. Bolland and Gee arbitrarily took 15 instead of 17·5 kcals., and since they used the value of the OH strength in water (110 kcals.) they calculated a greater exothermicity than here; (5) will be a strongly exothermic reaction. In olefinic systems [where also $E(CH)_{\alpha\text{-methylene}}$ may be less than 100], R may be sufficiently large (Bolland and Gee, *loc. cit.*) that (6) is also nearly, if not quite, exothermic. In paraffinic systems, however, R is probably small, so that it is difficult to escape the conclusion that (6) must be endothermic. It becomes necessary to suppose that if (6) occurs it does so with an activation energy, or else that the peroxide radical formed in (5) carries with it into (6) some of its energy of formation (it will certainly carry vibrational energy, since the OO distance increases when RO_2 is formed from O_2). In the latter case, much of the energy of peroxide decomposition may also be provided, thus accounting for the small yields of peroxides actually found.

Bolland (*Proc. Roy. Soc.*, 1946, *A*, **186**, 218) finds the energy of activation of (6) (where RH is ethyl linoleate) to be significantly in excess of that for (5), in agreement with the present discussion.

I am indebted to Dr. L. H. Long for stimulating discussion, and to Imperial Chemical Industries for the gift of a set of polythene atomic models.

LABORATORY OF PHYSICAL CHEMISTRY, CAMBRIDGE. [*Received, February 27th*, 1947.]

83. *Interactions between Non-bonded Atoms, and the Structure of* cis-*Decalin.*

By D. H. R. Barton.

An attempt has been made to calculate the energy differences between the staggered and the opposed form of ethane, between the boat and the chair form of *cyclo*hexane, and between *cis*- and *trans*-decalin. In each case the results are in qualitative agreement with experiment. The calculations support the formulation (III) for *cis*-decalin as compared with the Sachse–Mohr structure (II).

The important part that the phenomena of steric hindrance play in chemistry is well appreciated, and any method that promises its evaluation in a quantitative or even semi-quantitative way is well worth attention. A semi-quantitative attempt at the calculation of such effects has been given by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173; compare A. G. Evans, *Trans. Faraday Soc.*, 1946, **42**, 719 : Westheimer and Mayer, *J. Chem. Physics*, 1946, **14**, 733) for the symmetrical S_N2 mechanism of alkyl halide substitution. The following treatment is based on a simple adaptation of their ideas.

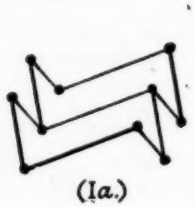
For substances not containing dipoles the interaction energy, I.E., between non-bonded atoms may be expressed by equations of the types

$$\text{I.E.} = \Sigma\psi_{ij} = \Sigma\left(\frac{-a}{r_{ij}^{6}} + be^{-\mu r_{ij}}\right) \quad \text{(i)}$$

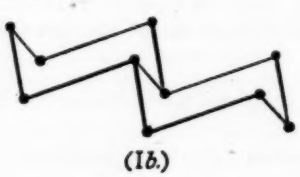
$$\text{I.E.} = \Sigma\psi_{ij} = \Sigma\left(\frac{-a}{r_{ij}^{6}} + \frac{b'}{r_{ij}^{12}}\right) \quad \text{(ii)}$$

in which ψ_{ij} is the interaction energy between a pair of non-bonded atoms, r_{ij} is the distance apart of the nuclei of the pair, and a, b, μ, and b' are constants. The first term, $-a/r_{ij}^{6}$, represents the dispersion energy, of which the constant a can be calculated from London's formula (*Trans. Faraday Soc.*, 1937, **33**, 8), whilst the second represents the repulsion energy resulting from the interpenetration of electronic sheaths. Unfortunately, there is considerable uncertainty as to the precise evaluation of this second term. If the repulsion expression of equation (i), the form of which is in agreement with quantum-mechanical considerations, be employed, then μ, for saturated hydrocarbons, may be set equal to 4·6, this being the same as the corresponding constant of the exponential repulsion term for helium atoms (Slater and Kirkwood, *Physical Rev.*, 1931, **37**, 682). If, however, the repulsion term, as in equation (ii), is assumed to vary as r_{ij}^{-12} as suggested by Hill (*J. Chem. Physics*, 1946, **14**, 465), then b' can be calculated by putting $\mathrm{d}\psi_{ij}/\mathrm{d}r_{ij} = 0$ when $r_{ij} = r_{0ij}$, the sum of the van der Waals radii of the pair of non-bonded atoms under consideration. The constant b of equation (i) can be obtained in the same way as b' once a value for μ has been assumed.

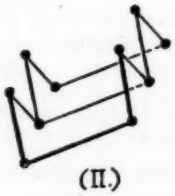
In order to test the validity of such equations, calculations with saturated hydrocarbons seem particularly attractive, and in some cases there are quantitative checks on the accuracy of the figures obtained. By summing the interaction energy between every possible pair of non-bonded atoms, some attempt at the evaluation of the energy differences, $\Delta\Sigma\psi_{ij}$, between the staggered and the opposed form of ethane, between the boat and the chair form of *cyclo*hexane, and between *cis*- and *trans*-decalin has been made. The results are set out in the table. In the case of *cis*- and *trans*-decalins it is necessary to consider the novel form of the *cis*-compound recently proposed by Bastiansen and Hassel (*Nature*, 1946, **157**, 765) on the basis of electron-diffraction measurements. *trans*-Decalin may be represented by the formulæ (I*a*)



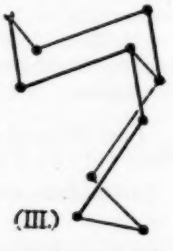
(I*a*.)



(I*b*.)



(II.)



(III.)

or (I*b*) which are identical, and *cis*-decalin by the Sachse–Mohr formula (II) or by the recently proposed formula (III).

A van der Waals radius of 1·6 A. has been used for carbon but, as there is some uncertainty about this radius for hydrogen, the calculations have been made with both the value 1·2 A., preferred by Pauling (" Nature of the Chemical Bond ", p. 187), and the value 1·3 A. suggested by Mack (*J. Amer. Chem. Soc.*, 1932, **54**, 2141). Certainly a larger van der Waals radius for hydrogen could not be justified. Application of the formula proposed by Dostrovsky, Hughes, and Ingold (*loc. cit.*) for the variation of van der Waals radii has not been made in detail, but such corrections would certainly not alter qualitatively the stability order; indeed, with ethane, the quantitative differences in $\Delta\Sigma\psi_{ij}$ produced thereby are small. In any case the reasons for using this formula are not compelling.

Substance.	Differences in non-bonded interaction energy. $\Delta\Sigma\psi_{ij}$ in kcals.				Stability order as shown by $\Delta\Sigma\psi_{ij}$.
	$be^{-4\cdot 6r_{ij}}$ repulsion term.		$b'r_{ij}^{-12}$ repulsion term.		
	$r_{0HH} = 2\cdot4$ A.	$r_{0HH} = 2\cdot6$ A.	$r_{0HH} = 2\cdot4$ A.	$r_{0HH} = 2\cdot6$ A.	
Ethane	0·09	0·27	0·09	0·39	Staggered > opposed
*cyclo*Hexane	1·31	2·47	2·73	6·85	Chair > boat
trans- and *cis*-Decalin, (I) and (II)	3·39	4·55	5·29	15·51	*trans* > *cis*
trans- and *cis*-Decalin, (I) and (III)	0·52	3·06	3·48	8·23	*trans* > *cis*
cis-Decalin, (II) and (III) ...	2·87	1·49	1·81	7·28	(III) > (II)

A number of interesting points arise from the table of calculated energy differences. First, while the stability order for ethane is qualitatively in agreement with that now generally accepted, the energy differences are all far too small to correspond to the observed energy barrier of about 3 kcals. (compare Eyring, *J. Amer. Chem. Soc.*, 1932, **54**, 3191). Since the existence of this high energy barrier has been confirmed by so much evidence, including precision heat-of-combustion data (see, *e.g.*, Spitzer and Huffman, *ibid.*, 1947, **69**, 211; Pitzer, *Science*, 1945, **101**, 672), it must be admitted that the potential functions used here are inadequate for quantitative calculation, at least in the case of ethane. It is very difficult, nevertheless, to see how the repulsion terms of equations (i) and (ii) could be modified in any reasonable manner, whilst retaining a hydrogen van der Waals radius of 1·2—1·3 A., so as to give agreement with experiment. This was doubtless appreciated by Aston *et al.* (*J. Chem. Physics*, 1944, **12**, 336), who showed that the observed energy barriers in organic molecules could be accounted for by an empirical expression for the interaction energy, (iii), containing only a repulsion term. In this expression k is an arbitrarily assigned constant chosen to give agreement with experiment.

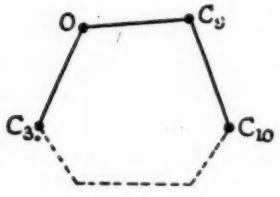
$$\text{I.E.} = \Sigma\psi_{ij} = \Sigma\frac{+k}{r_{ij}^{6}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(iii)}$$

This is very different from any of the previously proposed functions, such as those given by (i) and (ii), which have some theoretical support.

Secondly, the stability order for *cyclo*hexane is in agreement with the view generally held, but the energy differences are much lower than those anticipated on the basis of Aston's equation (iii) (compare Kumler, *J. Amer. Chem. Soc.*, 1945, **67**, 1901) and the known energy barrier in ethane.

Thirdly, the calculations support the claim of Bastiansen and Hassel (*loc. cit.*) that *cis*-decalin is to be represented by (III) rather than (II). By using Aston's empirical function (iii), the greater stability of (III) over (II) would be much enhanced. A direct check with the *trans*- and *cis*-decalins is possible from the observed difference of about 5 kcals. in the heats of combustion, *trans*-decalin being the more stable isomer in agreement with calculation. It will be seen that the use of the $b'r_{ij}^{-12}$ repulsion term and of a van der Waals radius of 1·2 A. for hydrogen gives satisfactory agreement with experiment, though this is not of great significance in view of the interaction energy minimising factors discussed below. It is noteworthy that the interesting 3(α) : 9(α)-epoxy-compounds, for example 3(α) : 9(α)-epoxy-Δ^{11}-cholenic acid methyl ester (IV), prepared by Kendall and his collaborators (*J. Biol. Chem.*, 1946, **164**, 569), are most probably to be formulated as derived from a modified form of (III), shown with part of the rest of the steroid molecule in (V), by conversion of ring A of the cholane skeleton into the boat form of *cyclo*hexane. The very small amount of angle strain required for the formation of these epoxy-compounds on the basis of formula (V) is shown in the scale drawing (VI), which represents a plane cut through the steroid molecule to include C_3, C_9, C_{10}, and the oxygen bridge. Formulation of these

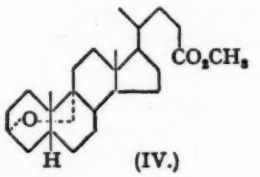
compounds from the Sachse–Mohr *cis*-decalin (II) would require an impossible extension of valency bonds or distortion of valency angles. It is also possible to satisfy steric requirements



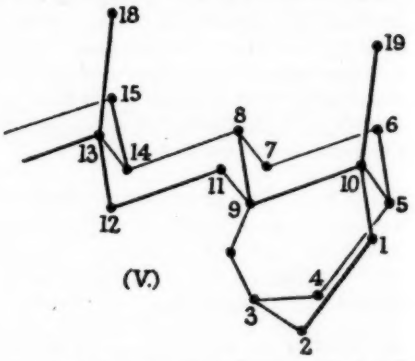
(VI.)

Angle strain :

$C_9\widehat{O}C_3 \sim 8°$, $O\widehat{C}_9C_{10} \sim 3°$.



(IV.)



(V.)

and at the same time to formulate these epoxy-compounds as derived from a two-boat *cis*-decalin not identical with (II) (see Shoppee, *Ann. Reports*, 1946, **43**, 200). Although this formulation is equally probable geometrically, it is less probable from the energetic view point and so is not illustrated here. This alternative structure preserves the special peculiarity of (III), namely that the configurations of the valencies about the C_9 and C_{10} atoms (decalin enumeration) are staggered, whereas in the conventional Sache–Mohr *cis*-decalin (II) they are opposed.

It is, of course, appreciated that while the form (III) of *cis*-decalin is more stable than (II) in solution or in the gas phase, this does not necessarily imply that it will be packed more conveniently into a crystal lattice, for in the lattice non-bonded interactions of atoms with those of the neighbouring molecules may play a dominant part.

The calculations on the basis of equations (i) and (ii) have assumed the constancy of covalent bond lengths and of the tetrahedral angle. Strictly speaking, this is not justified because the extension of valency bonds and especially the flexing of valency angles will lead to a minimising of the calculated energy differences. Although this would not alter qualitatively the calculated order of stabilities, it would lead to an appreciable quantitative diminution of the values of $\Delta\Sigma\phi_{ij}$. This is specially so because the calculated energy differences are chiefly dependent on strong repulsive interaction between a few pairs of atoms, for example between the pair of upper hydrogen atoms attached to C_1 and C_4 in the case of the boat form of *cyclo*hexane. In view, however, of the fact that these considerations cannot account for the failure of the potential functions of equations (i) and (ii) in explaining quantitatively the high energy barrier to rotation in ethane, it would be pointless to extend the calculations in this manner at present. Indeed, until this energy barrier can be evaluated quantitatively, it would seem that calculations of the type made in this paper must be regarded as having only qualitative significance.

Added February 20th, 1948. Since this paper was submitted for publication Westheimer (*J. Chem. Physics*, 1947, **15**, 252) has reported the calculation of the activation energy for the racemisation of 2 : 2′-dibromodiphenyl-4 : 4′-dicarboxylic acid, using, in part, a similar approach to the one adopted here. For the constant μ of the exponential repulsion term in equation (i) above Westheimer selects a value of 6·06. Both this value and the one, 4·6, employed here are considerably higher than that, 2·9, adopted by Dostrovsky, Hughes, and Ingold (*loc. cit.*). Indeed, the non-bonded interaction energy equation of the latter authors cannot be applied in the general case because, in the absence of dipolar interaction, it gives attractive potentials at *all* values of r.

I thank Dr. C. W. Shoppee for an interesting discussion. Part of this work was carried out during the tenure of an Imperial Chemical Industries Research Fellowship.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W. 7.

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84. *The Mechanism of Oxidation of Monoethenoid Fatty Acids and Esters. The Course of Thermal Catalytic Oxidation of Methyl Oleate.*

By J. H. Skellon.

Highly purified methyl oleate was oxidised at 120° by gaseous oxygen in the presence of a vanadium catalyst, under conditions which resulted in little or no disruption or dimerisation of the carbon chain.

The initial attack by oxygen appears to take place mainly at the ethenoid linkage but the hydroperoxide undergoes rapid transition at this temperature and the final oxidation products are more complex.

The neutral non-disrupted oxidation products were separated and examined directly, without study of the scission products. They consisted chiefly of an oily monomeric complex of approximate composition $C_{19}H_{36}O_6$, in which one molecular proportion of oxygen is considered to be present as an irreducible peroxide, and a smaller proportion of a compound identifiable with isomeric hydroxy-keto-stearates.

The structure of the complex is discussed and a mechanism is advanced to account for the changes occurring during gaseous oxidation of monoethenoid fatty acids and esters.

Atherton and Hilditch (*J.*, 1944, 105) showed that during autoxidation of methyl oleate at 20° and 120°, attack by oxygen at the methylene groups adjacent to the ethenoid bond was much less at 120° than at 20°. At the higher temperature, Gunstone and Hilditch (*J.*, 1945, 836) observed that peroxidation occurred mainly at the ethenoid group. Swern, Scanlan, and Ault (*J. Amer. Chem. Soc.*, 1945, **67**, 1132), as a result of prolonged oxidation at 65°, separated an oxidation product of methyl oleate consisting partly of methyl monohydroxy-esters of one or more monomeric unsaturated acids in which the ethenoid linkage had apparently migrated from the 9 : 10-position.

These investigations indicate that in thermal oxidation of methyl oleate, oxygen attack may take place additively and substitutively in varying degree. At moderate temperatures (below 35°) such reactions may be similiar to the photochemical oxidations of methyl oleate carried out first by Farmer and Sutton (*J.*, 1943, 119) and later by Swift, Dollar, and O'Connor (*Oil and Soap*, 1946, **23**, 355), from which it is suggested that the primary oxidation product is a mixture of 8- and 11-hydroperoxido-octadecenoic acids.

It has become increasingly doubtful whether a mechanism involving oxygen attack at a methylene group adjacent to the ethenoid linkage is applicable to thermal oxidations; the experimental work to be described lends support to the view, recently expressed by Gunstone and Hilditch (*J.*, 1946, 1023) and Hilditch (*J. Oil Col. Chem. Assoc.*, 1947, **30**, 1), that original entry of oxygen into the unsaturated system must be at the double bond.

Although it seems conclusive that the initial oxidation product is a hydroperoxide as opposed to a cyclic peroxide, it is by no means certain whether the isomeric forms are either (*a*) 10-hydroperoxido-octadec-8-enoate and 9-hydroperoxido-octadec-10-enoate or (*b*) 11-hydroperoxido-octadec-9-enoate and 8-hydroperoxido-octadec-9-enoate.

Thermal oxidation results in the disappearance of peroxidic oxygen, but little is known concerning the exact nature of the hydroperoxide transition product and the structure of the non-disrupted oxidised carbon chain.

In the present investigation, changes occurring at various stages of oxidation in the C_{18} chain before disruption have been studied, and a mechanism is advanced to account for such changes. Highly purified methyl oleate was oxidised by gaseous oxygen at 120° in the presence of a vanadium or cobalt catalyst, under conditions adjusted to give a maximum oxidation without rupture of the carbon chain. After 6 hours, the peroxide oxygen content reached a maximum at only 16% of the theoretical value (Calc. for $C_{19}H_{36}O_4$: 4·88% active oxygen), thereafter decreasing steadily. Extensive thermal catalytic oxidations of the ester and the parent acid have shown that, under such conditions, the initial peroxides rapidly undergo changes into secondary oxidation products.

During the transition phase (marked by peroxide decomposition) there was little evidence of abnormal changes in the rate of decrease of unsaturation, that in the first 6 and in the last 4 hours being 9·6 and 7·8 units per hour, respectively. The observed fall in iodine value was considerably greater than that required for exclusive formation of peroxide at the ethenoid linkage, and it was evident that the secondary reactions prevailing at 120° preclude any simple relationship between the observed iodine value and that calculated on the above assumption. The increase in free acidity was comparatively small up to 10 hours.

The conditions of oxidation resulted in little or no dimerisation, whilst the small percentage

of carbon destroyed (considerably less than 1 atom per mol. of ester) indicated no extensive disruption of the carbon chain. The amount of oxygen ultimately consumed was greater than that required for a hydroperoxide or isomeric derivative. Such changes were invariably observed during numerous catalytic oxidations of the ester and of oleic acid, the stage at which peroxidic oxygen formation was at a maximum being dependent on the conditions of oxidation. These observations partly afford an explanation of the apparently anomalous results noted by many workers during the atmospheric oxidation of glycerides and fats at various temperatures.

The detailed oxidation data are given in Table I. Peroxide values are expressed as % of active oxygen [Calc. for $C_{19}H_{36}O_4$: 4·88% active oxygen = 9·76% total peroxidic oxygen (Farmer and Sutton) = 3050 ml. of 0·002N-thiosulphate per g. (Atherton and Hilditch) = 6100 milli-equivs. per kg. (Swift, Dollar, and O'Connor, *loc. cit.*)].

From data available, comparative peroxide values obtained during oxidations by various authors are expressed in terms of active oxygen:

(i).	(ii).	(iii).	(iv).
Farmer and Sutton (*loc. cit.*).	Gunstone and Hilditch (*J.*, 1945, 836).	Author.	Swift, Dollar, and O'Connor (*loc. cit.*).
0·64% (photochemical, 4 hrs.).	120° (4 hrs.). 1·17% (max.). 0·77% (7 hrs., decreasing).	120° (4 hrs., catalytic). 0·56% (increasing). 0·54% (7 hrs., decreasing).	0·24% (photochemical, 30 hrs.).

The Oxidation Products.—The yellowish-red oily oxidation product at 6 hours, containing the maximum peroxidic oxygen attained, gave *M*, 333 (Calc. for $C_{19}H_{36}O_4$: *M*, 328). After 10 hours, it contained little free peroxidic oxygen (0·2% active oxygen), and was almost saturated. Qualitative tests indicated the presence of ketonic derivatives. The neutral product (85%) was separated and examined in order to ascertain the precise nature of the peroxide transition.

Successive treatment with large volumes of light petroleum at low temperature resulted in recovery of a semi-crystalline product (25%), completely saturated and containing no appreciable amount of peroxidic oxygen. Analysis showed that it contained one carbonyl group per mol., and was apparently identical with a mixture of isomeric 9-hydroxy-10-keto- and 10-hydroxy-9-keto-stearates. Comparative analysis of specimens of such isomeric hydroxyketostearic acids, prepared from oleic acid by the method of King (*J.*, 1936, 1788), confirmed the nature of the product.

Catalytic thermal oxidation of methyl oleate appears to result in partial transition of the hydroperoxide grouping to the grouping $-CO\cdot CH(OH)-$ but the comparatively low yield of this oxidation product indicated either that concurrent changes occur or that the neutral ketol in turn undergoes further transition. The main oxidation product was therefore examined for presence of neutral monoxides or dihydroxy-derivatives. Methyl oxido-oleate and oxido-elaidate were not found in the product of thermal catalytic oxidation at 120°; under these conditions there seem to be little grounds for the supposition that epoxy-compounds of this nature result from interaction between peroxide and ethenoid linkage. Ellis (*Biochem. J.*, 1936, **30**, 753) isolated oxido-oleic and -elaidic acids from the autoxidation products of elaidic and oleic acids at moderate temperature (60—70°), and Dorée and Pepper (*J.*, 1942, 477) obtained oxido-brassidic acid during catalytic oxidation of erucic acid at 70° and 120°.

This isolation of oxido-acids from the products of catalytic oxidation of three mono-ethenoid acids at temperatures between 60° and 120° is significant, as it has a direct bearing on the mechanism of autoxidation. It is possible that neutral oxido-derivatives if formed are less easy to isolate; on the other hand, it is difficult to reconcile this with modern views that epoxy-compounds are not formed in the oxidation and polymerisation of the parent oils.

The absence of appreciable amounts of neutral dihydroxy-derivatives was also confirmed; the non-disrupted oxidised product consisted largely of an oily complex together with a minor proportion of the neutral ketone.

The Complex Oxidation Product.—The residual dark brown oil (60%) was almost saturated and contained only a small percentage of peroxidic oxygen capable of liberating iodine from potassium iodide. On strong heating in a vacuum, this peroxidic oxygen disappeared and there was some evidence of disruption. Analysis indicated a main monomeric constituent of approximate composition, $C_{19}H_{36}O_6$, very resistant to the action of boiling alcoholic potash; it appeared to be a neutral analogue of the complex obtained during catalytic oxidation of oleic acid (see Skellon, *J. Soc. Chem. Ind.*, 1931, **50**, 382T).

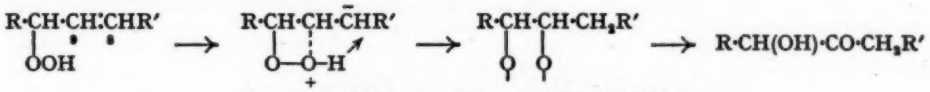
Further examination of the products obtained by oxidising oleic acid at 120° with various

catalysts has confirmed that breakdown into cleavage products is not extensive up to 7 hours. No free dihydroxystearic, oxido-oleic, or oxido-elaidic acids were found, but there was evidence of the presence of minor proportions of ketones in the material separated from light petroleum at low temperature. The complexes were partly broken down by alcoholic potash, affording small quantities of dihydroxystearic acid, m. p. 132°, and acids of high equivalent weight similar to those formerly described (Skellon, *loc. cit.*).

The oily complex is invariably obtained during autoxidation of monoethenoid acids and esters; similiar products have also been observed during atmospheric oxidation of fats at high temperature. It is considered that at least one type may be formed as the result of enolisation of a $^{-}CO{\cdot}CH(OH)^{-}$ group at temperatures above 100° with subsequent further entry of oxygen; ultimate dimerisation or polymerisation may be due to cross linkage between such molecules, and is not due to formation of epoxides.

A Mechanism of Gaseous Oxidation of Methyl Oleate applicable to Monoethenoid Fatty Acids and Esters.—The course of catalytic oxidation of methyl oleate is considered to take place as follows: (1) Initial attack by oxygen at the ethenoid bond, with formation of the 9-hydroperoxido-octadec-10-enoic and 10-hydroperoxido-octadec-8-enoic esters suggested by Gunstone and Hilditch (*J.*, 1946, 1023).

(2) Intermediate transition of the hydroperoxides to isomeric hydroxyketostearates, with consequent diminution in peroxidic oxygen content:

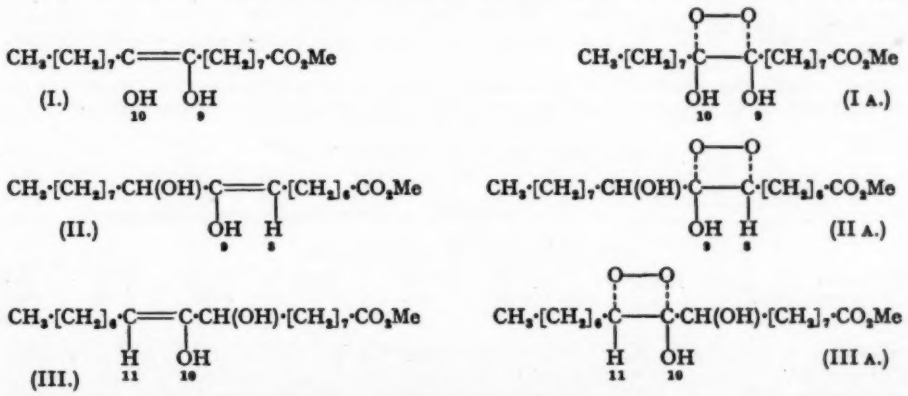


$(R = CH_3{\cdot}[CH_2]_7- ;\ R' = -[CH_2]_6{\cdot}CO_2Me.)$

(3) The isomeric ketol carboxylic esters enolise or rearrange in thermal oxidations, and further entry of oxygen results in formation of a monomeric complex containing " bound " peroxidic oxygen not reducible by interaction with potassium iodide:

$$CH_3{\cdot}[CH_2]_7{\cdot}CO{\cdot}CH(OH){\cdot}[CH_2]_7{\cdot}CO_2Me \rightleftharpoons CH_3{\cdot}[CH_2]_7{\cdot}CH(OH){\cdot}CO{\cdot}[CH_2]_7{\cdot}CO_2Me$$

may thus give rise to (I), (II), or (III). The further entry of oxygen thus results in complexes ($C_{19}H_{36}O_6$) which may have the possible structures (IA), (IIA), or (IIIA). The mode of



attachment of the " bound " peroxidic groups (shown by dotted lines) may or may not involve a cyclic structure. Subsequent oxidation of (IIA) and (IIIA) would result in formation of a carbonyl group at the 10 and the 9 position respectively, giving a product, $C_{19}H_{34}O_6$.

Breakdown of these complexes at the 9 : 10-, 8 : 9-, and 10 : 11-positions would account for the various scission products obtained by different authors: (*a*) nonoic and azelaic acids from (IA), (*b*) suberic and ketodecoic acids from (IIA), (*c*) octoic and oxalic acids from (IIIA). The reported presence of irreducible peroxides in fats submitted to atmospheric oxidation at high temperature may be accounted for by formation of complexes of a similiar character.

It is noteworthy that application of the mechanism to the alternative attack by oxygen at methylene groups adjacent to the ethenoid linkage could result in formation of 8 : 9- and 10 : 11-ketol carboxylic esters, eventually giving rise to complexes not very dissimiliar in structure, but more resistant to further attack by oxygen. The possibility of both reactions

proceeding concurrently under certain conditions cannot be excluded in the light of present knowledge.

Experimental.

Methyl Oleate.—The ester used was prepared from oleic acid (purified as described by Skellon, *J. Soc. Chem. Ind.*, 1931, **50**, 131T), the amount recovered being 88%; b. p. 165—166°/3—5 mm. (Found: equiv., 296; I.V., 87·3. Calc. for $C_{19}H_{36}O_2$: equiv., 295; I.V., 85·8). Samples not sealed under an inert gas absorbed atmospheric oxygen slowly at room temperature (Found, after 24 hrs., 6 months, and 12 months: I.V., 77·5, 70·1, 68·8, respectively). The last specimen then contained 1% of peroxidic oxygen expressed as active oxygen.

Catalytic Oxidations.—The oxidation apparatus consisted of a wide-mouthed glass container fitted with a Bakelite cover, through which passed a bell-shaped perforated stirrer, together with an inlet tube for oxygen terminating as a jet inside the hollow dome. Constant temperature was maintained by use of the usual thermostatic temperature control in an oil-bath. The delivery of a slow stream of dry oxygen at the jet with rotation of the special stirrer at high speed ejected a fine spray of oil and gas bubbles through the perforations, thus ensuring intimate mixing. Carbon dioxide evolved was absorbed in baryta solution. The purified freshly distilled ester (48 g.) containing sufficient vanadium oleate to provide 0·02% of vanadium was oxidised at 120° for 10 hours. A similiar oxidation was carried out using 0 03% of cobalt (as oleate) as catalyst. The results are given in Table I (Calc. for $C_{19}H_{36}O_4$: active oxygen, 4·88%). Peroxide values were determined iodometrically; control determinations were carried out simultaneously on pure benzoyl peroxide.

Table I.

Catalytic oxidation of methyl oleate at 120°.

Time (hours).	1.	4.	6.	10.
	(Catalyst, 0·02% V as oleate.)			
Iodine value (Wijs)	71·9	52·7	29·3	8·6
Fall in iodine value	15·4	34·6	58·0	78·6
Rate of fall (units per hour)	15·4	8·5	9·6	7·8
Acid value	—	10·5	19·7	35
Sap. value	215·6	221·1	228·0	292·0
Peroxide value (% active oxygen)	—	—	—	0·3
	(Catalyst, 0·03% Co as oleate.)			
Peroxide value	0·42	0·57	0·76	0·40
Peroxide value (as % of theoretical)	8·7	11·6	15·5	8·3

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Peroxide values taken at hourly intervals	0·42	0·48	—	0·57	0·63	0·76	0·54	—	0·41	0·40

In order to verify the general trend of peroxide changes, a series of gaseous oxidations was carried out with pure oleic acid, the peroxidic oxygen content being determined at regular intervals. Typical data were:

Catalytic oxidation of oleic acid at 120°.

Time (hours).	1.	2.	3.	4.	5.	6.	7.
Catalyst	(0·05% of metal as oleate or naphthenate)						
	Peroxide-oxygen, % active oxygen.						
Vanadium	0·22	0·33	0·38	0·40	0·57	0·34	0·20
Cobalt (naphthenate)	—	0·51	—	—	0·60	0·78	0·26
Barium	—	0·86	—	—	0·92	—	0·35

Examination of Oxidation Products.—The oxidised ester (6 hours, 120°, 0·02% V) was a yellowish-red oil soluble in alcohol, chloroform, carbon tetrachloride and warm light petroleum [Found: acid value, 19·7; sap. value, 228; I.V., 19·7; peroxide value, 0·28%; *M* (Menzies–Wright), ebullioscopic in chloroform, 333; in carbon tetrachloride, 308. Calc. for $C_{19}H_{36}O_4$: *M*, 328]. At 10 hours the same specimen was darker and more viscous (Found: I.V., 8·6; acid value, 35; sap. value, 292; peroxide value, 0·2%).

The Neutral Oxidation Product.—The oxidised ester (10 hours, 120°, 0·02% V) was washed with a 20% solution of sodium carbonate, the alkaline liquors being repeatedly extracted with ether; 25·1 g. (84%) of a neutral product were recovered (Found: I.V., 8·3; sap. value, 267; peroxide value 0·2%). It gave qualitative tests for ketols.

10 G. were dissolved in 100 ml. of chloroform and cooled below 0° for 24 hours. No dihydroxystearate separated. The chloroform was removed, and the residue warmed with 400 ml. of light petroleum and cooled well below 0° for 36 hours. After filtration of the ice-cold petroleum, there remained 0·3—0·4 g. (3%) of a white crystalline deposit on the sides of the vessel, and 2·5 g. (25%) of a semi-solid product. The former was identified as methyl dihydroxystearate not previously separated by use of chloroform; m. p. 68° [Found: *M* (Rast), 325. Calc. for $C_{19}H_{38}O_4$, methyl dihydroxystearate: *M*, 330]. The m. p. of methyl dihydroxystearate is 71°. The semi-solid product melted at a lower temperature and gave qualitative tests for a ketone. It was again treated with light petroleum at 0° and attempts were

made to crystallise it from dilute alcohol. Analysis gave the following results: Found: I.V., 3·5; peroxide value, 0·1%; C, 69·65; H, 10·86; >CO, 10·4; *M* (Menzies–Wright), ebullioscopic in chloroform, 330. Calc. for $C_{19}H_{36}O_4$: C, 69·50; H, 10·97%; *M*, 328; 1 >CO per mol., 8·5%; 2 >CO per mol., 17·1%).

Control determinations of carbonyl content were carried out simultaneously on a specimen of isomeric 9-hydroxy-10-keto- and 10-hydroxy-9-keto-stearic acids prepared from oleic acid by King's method (*J.*, 1936, 1788) (Found: >CO, 8·8%; peroxide value, 0; *M*, by titration, 312. Calc. for $C_{18}H_{34}O_4$: *M*, 314; 1 >CO, 8·9%). The m. p. was 64—65°.

Specimens (10 g.) of the neutral product were examined for the presence of neutral oxido-oleates or oxido-elaidates, by adaptation of Ellis's method (*loc. cit.*) for isolation of the parent oxido-acids during autoxidation of elaidic acid. No neutral oxido-derivatives were isolated.

The neutral product was further examined for presence of methyl dihydroxystearate. 5 G. were dissolved in acetone and left below 0° for 72 hours, but no crystalline material separated. On repetition of the process with minimal amounts of solvent, 0·3 g. of semi-crystalline material was recovered and hydrolysed (Found: I.V., 0; equiv., 359). The 0·3 g. of semi-crystalline material was therefore not methyl dihydroxystearate, which would give a dihydroxystearic acid of m. p. 132° or 95°.

The Complex Neutral Oxidation Product.—The bulk light petroleum mother-liquors after separation of the ketol carboxylic ester from 10 g. of oxidised methyl oleate (10 hours, 120°, 0·02% V) were evaporated down, affording 6 g. (60%) of a yellowish-brown oil (Found: acid value, 17; I.V., 8·2; sap. value, 280; peroxide oxygen content, 0·5%). On strong heating in a vacuum, the small peroxidic oxygen content disappeared and there was an odour of aldehydic products. The oil saponified with difficulty on prolonged boiling with alcoholic potash, giving sap. equiv., 201, indicating only partial disruption.

A second specimen of these oily products was obtained from the neutral oxidation product obtained during a similar oxidation of methyl oleate, 0·03% of cobalt being used as catalyst. 7 G. of oxidised methyl oleate (10 hours, 120°, 0·03% Co) were dissolved in 50 ml. of chloroform and kept for 48 hours below 0°. As no solid separated, the chloroform was removed, and the residue dissolved in 200 ml. of light petroleum and cooled below 0° for 60 hours. 1·4 G. (20%) of semi-crystalline product were recovered (Found: I.V., 19·3; peroxide value, 0·59%; C, 69·49; H, 10·89. Calc. for $C_{18}H_{34}O_4$: C, 69·50; H, 10·97%). This product gave qualitative tests for ketols, and appeared to be similiar to the keto-derivative obtained in the oxidation using 0·02% V as catalyst.

Evaporation of the light petroleum mother-liquors resulted in recovery of 4·5 g. (64%) of a yellowish-brown oily product (Found: I.V., 26·7; sap. equiv., 227·5; peroxide value, 0·5%; C, 60·01; H, 9·41. Calc. for $C_{18}H_{36}O_6$: C, 63·3; H, 10·0%).

Acidic Oxidation Products.—After removal of the neutral product from 30 g. of oxidised methyl oleate (10 hours, 120°, 0·02% V), the alkaline extracts were boiled with excess of alcoholic potash. On acidification and extraction with ether, 3 g. (10%) of mixed acidic products were recovered [Found: I.V., 15; equiv., 158. Calc. for $C_9H_{18}O_2$: equiv., 158. Calc. for $C_9H_{18}O_2 + C_9H_{16}O_4$ (monobasic and dibasic acid): mean equiv., 126].

Comparative Catalytic Oxidations of Oleic Acid.—A series of oxidations were carried out on the pure parent acid, using the same catalysts—vanadium and cobalt—and the same conditions of oxidation. Analytical data for the products at 7 hours, 120°, are given in Table II. These results indicated that the

TABLE II.

Catalytic oxidation of oleic acid (7 *hours*, 120°).

Catalyst, % (oleate).	Acid value.	I.V.	Peroxide value.	Sap. value.	Analysis. C, %.	H, %.	Calc. for:	C, %.	H, %.
V, 0·04	172·4	50·7	0·20	243·6	68·0	10·29	$C_{18}H_{34}O_4$	68·8	10·82
V, 0·08	161·4	20·1	0·16	283·6	62·04	9·15	$C_{18}H_{34}O_6$	62·43	9·83
Co, 0·05 (naphthenate)	170·6	47·9	0·26	245·2	68·69	8·83	$C_{18}H_{34}O_4$	68·8	10·82
Co, 0·05	169·7	38·3	0	260·0	62·32	9·20	$C_{18}H_{34}O_6$	62·43	9·83
Co, 0·05	—	—	—	—	61·66	9·41	$C_{18}H_{34}O_6$	62·43	9·83

final products in the more efficient short gaseous oxidations of oleic acid had an approximate composition, $C_{18}H_{34}O_6$. Qualitative tests indicated the presence of small proportions of ketones. The products were saponified with difficulty, the ultimate products being dihydroxystearic acid, m. p. 132° (5—7%), and oxidised acids of high equivalent—indicating only partial disruption into scission products.

Oxidised oleic acid (0·05% Co as naphthenate), 7 hours 120°: no free dihydroxystearic acid was separable. 10 G. were dissolved in light petroleum; after standing at 0° for 24 hours, 2 g. (20%) of semicrystalline material were recovered (Found: acid value, 181; equiv., 347·3; I.V., 25·8). After evaporation of the light petroleum an oily residue (6—7 g.) was recovered (Found: mean equiv., 343. Calc. for $C_{18}H_{34}O_6$: 346).

Oxidised oleic acid (0·05% Co as oleate, 7 hours' oxidation at 120°): 6 g. were saponified on prolonged boiling with alcoholic potash. After removal of alcohol, acidification and extraction with light petroleum and ether, there were recovered: 2·5 g.(42%) of acids soluble in light petroleum (Found: mean equiv., 290), 2·4 g.(40%) of brown oily oxidised acids soluble in ether (Found: equiv., 306), and 0·3—0·4 g.(5%) of white solid acids, which were recrystallised from alcohol (Found: equiv., 314. Calc. for dihydroxystearic acid, $C_{18}H_{36}O_4$: equiv., 316); m. p. 131—132° (lit., 131—132°).

CHELSEA POLYTECHNIC, S.W. 3. [*Received, April 25th*, 1947.]

85. *The Decomposition Reactions of the Aromatic Diazo-compounds in Aqueous Solution explained on Simple Electronic Theory, and without Recourse to the Current Free-radical Hypothesis.*

By Herbert H. Hodgson.

One electronic mechanism only is shown to be sufficient to explain: *s*-azo-compound formation in acid, neutral, or alkaline media; the Gomberg and similar reactions in which *s*-diaryls are not formed and in which invariability of *op*-substitution occurs; the conversion of 2 : 2′-tetrazodiphenyl into dibenzopyridazine (diphenylazone) and carbazole; the reactions of diazobenzene hydroxide in faintly alkaline solution with carbon disulphide, *cyclo*hexane, and without added solvent; and numerous oxidations by diazo-compounds. The alternative free-radical hypothesis with its inherent difficulties is discussed and found to be entirely unnecessary, if not invalid, for the interpretation of the decompositions of aromatic diazo-compounds in aqueous solution.

A mechanism for the formation of symmetrical azo-compounds in acid solution with cuprous hydroxide as a reducing agent was first proposed by Hodgson, Leigh, and G. Turner (hereinafter referred to as H. *et al.*) (*J.*, 1942, 744) and supported by considerable experimental evidence. It postulated two stages, *viz.*, (1) formation of an aryl from a diazo-radical which in turn was formed from a diazonium ion by acceptance of an electron from the reducing agent, $Ar\cdot\overset{+}{N}\equiv N: + e \longrightarrow Ar\cdot\dot{N}=\dot{N}^{*} \longrightarrow Ar^{*} + N_2$; (2) union of the aryl with another diazo-radical, $Ar\dot{N}=\dot{N}^{*} + {}^{*}Ar \longrightarrow Ar{-}\dot{N}=\dot{N}{-}Ar$. (Dots represent electrons, an asterisk the single electron of a radical, and a dash a covalent link.) This mechanism has recently been adversely criticised by Saunders and Waters (hereinafter styled S. & W.) (*J.*, 1946, 1154), who regard it as improbable on the ground that the driving force in the homolysis of covalent diazo-compounds is the elimination of molecular, stable, nitrogen gas which leads to the simultaneous production of two neutral radicals. From the outset, therefore, S. & W. ignore the fact that ionic diazonium, not covalent diazo-compounds were concerned in the experiments of H. *et al.*

S. & W.'s mechanism is also two-staged, *viz.*, (1) production of the free aryl radicals by fission of two single links in a covalent diazo-compound, (2) union of the aryl radical with a dissociated diazo-kation (admitted therefore by S. & W. to exist in alkaline solution) which is first converted into a diazo-radical by the reducing agent, *i.e.*, by the H. *et al.* mechanism. S. & W.'s statement, that the mechanism of H. *et al.* is entirely different from their own, thus applies to stage (1) only, and raises the whole question of whether all the decomposition reactions of diazo-compounds in aqueous solution can be explained on simple electronic theory, or, alternatively, whether the hypothesis of free aryl radicals as advanced by Hey *et al.* (*J.*, 1934, 1799 *et seq.*) and Waters *et al.* (*J.*, 1937, 2007 *et seq.*) should be invoked (cf. *Ann. Reports*, 1937, **34**, 282; 1940, **37**, 250). This alternative will now be submitted to examination, in the course of which the validity of the free-radical hypothesis will be challenged and, in any event, its necessity denied (cf. also Kenner, *Nature*, 1945, **156**, 369).

S. & W.'s Hypothesis for the Formation of s*-Azo-compounds.*—S. & W. appear to postulate the free existence of radicals prior to subsequent reaction, and their origin to be the homolysis of undissociated diazo-hydroxide into two radicals with elimination of nitrogen, without the intervention either of a catalyst or of a reducing agent. In fact, the homolysis of $R{-}\dot{N}=\dot{N}{-}OH$ into R*, *OH, and N_2 does not involve electron acceptance of any kind. Two insuperable difficulties arise with this conception which its authors, although referring to them (cf. Hey, *J.*, 1934, 1801), do not attempt to explain, *viz.*, the non-formation of diaryl and of a phenol by the union of R* with *R and of R* with *OH, respectively. When, however, an aqueous solution of benzenediazonium chloride or sulphate is allowed to decompose spontaneously in the presence of calcium carbonate to maintain neutrality, the product is almost entirely a mixture of benzene-azo-, -bisazo-, and -trisazo-phenol (Hodgson and Marsden, *J.*, 1943, 379), and its origin is easily explained on simple electronic theory (*loc. cit.*). Similarly, when nitroso-acetanilide reacts with water the product is *p*-hydroxyazobenzene (Grieve and Hey, *J.*, 1934, 1797). These experiments would apparently afford far more evidence of free radicals than those quoted by S. & W. (*loc. cit.*) or by Hey for the Gomberg reactions (*loc. cit.*), where the absence of diphenyl or of phenol, under conditions which favour the formation of both, is surely proof that free phenyl and hydroxyl radicals do not exist prior to the actual reaction, but are involved, if at all, during the intermediate phase which precedes the final separation of the resultants. From Waters's own viewpoint (*J.*, 1937, 2015) that " neutral radicals are extremely

reactive entities which interact with practically the first molecule they encounter", the formation of diphenyl and of phenol with subsequent coupling to azophenol would certainly occur if covalent diazobenzene hydroxide decomposed in aqueous medium into C_6H_5* and *OH in the manner envisaged by S. & W. Apparently, however, S. & W. are content to believe that free phenyl and hydroxyl radicals can co-exist without any mutual effect on each other, but with truly remarkable activities towards any other substance that may be present: *e.g.*, in the Gomberg reaction the assumed free aryl radicals preferentially attack relatively unreactive molecules rather than combine with each other, and we have the extraordinary result that diazotised aniline will only form diphenyl if benzene be also present. This non-formation of symmetrical diaryls was also observed by Hodgson and Marsden (*J.*, 1940, 208), who employed stabilised diazonium salts for a great variety of Gomberg reactions in different media. In this connection, Waters (*J.*, 1937, 2014) cites the occurrence of diphenyl formation in the Bart reaction (see later) as to be expected if free aryl radicals are present during the course of the reaction.

Another weakness of the covalent homolysis theory is its comparative failure to account for the activity of the second radical as compared with that of the aryl radical. To the author, this predominant reactivity of the supposed aryl radical in diazo-decompositions is in itself evidence that only a diazonium ion is involved.

Finally, it must be emphasised that the arguments of S. & W. are all based on reactions of covalent diazo-compounds *in alkaline or neutral solution*, and that the experiments of H. *et al.* and the deductions therefrom are dismissed in six lines as improbable, notwithstanding the fact that the former were all conducted in strong acid solution and therefore under conditions where the diazonium ion would greatly predominate. This condition would also obtain in neutral solution owing to the relatively greater stability of the diazonium ion because of the resonance energy.

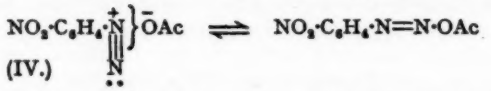
At this stage it is convenient to examine the main experimental evidence on which S. & W.'s hypothesis is based, especially as they state " that while previously the homolysis of undissociated diazo-compound into two free radicals with liberation of nitrogen was regarded as occurring regularly in non-dissociating solvents, there are now indications " that many diazo-compounds can be converted, in part at least, into free radicals in aqueous solution ".

The Reactions of Sodium Benzenediazoate (*the Gomberg Reaction*).—The author (*J. Soc. Dyers and Col.*, 1946, **62**, 199) has recently reviewed the work in this subject. At that time he accepted the free-radical mechanism, but contended that the origin of the free radicals was *via* the decomposition of diazonium kations and not by the fission of covalent diazo-compounds. Later consideration of the facts, including his own experimental work, has convinced him that the Gomberg reaction can be simply explained without any need for the existence of free radicals. Since nitrogen has to be evolved as :N≡N: before reaction occurs, it would appear more realistic to have it already in a triple-bonded condition and with only one link to be ruptured such as the diazonium ion provides, rather than with two links to sever such as the covalent diazo-compounds entail, *viz.*, R–N=N–X. Moreover, this viewpoint brings the Gomberg reaction into line with all the other reactions in which nitrogen is evolved, *e.g.*, replacement of nitrogen by hydrogen, hydroxyl, halogen, etc. Since the union of aryl nuclei in the Gomberg and similar reactions is stated to take place in acid media (cf. Hirsch, *Ber.*, 1890, **23**, 3705; 1892, **25**, 1196; Hodgson and Marsden, *J.*, 1940, 208; Elks, Haworth, and Hey, *J.*, 1940, 1284), neutral (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339; Gomberg and Pernert, *ibid.*, 1926, **48**, 1372) or alkaline media (previous references), it surely follows that the diazonium ion, which may be present exclusively in acid, and at all events will predominate in acid and neutral media (*loc. cit.*) while certainly existent in alkaline media to a variable extent, should be regarded as the necessary and sufficient reagent. In this connection, Hirsch (*loc. cit.*) in his preparation of hydroxydiphenyls by the interaction of diazotised aniline with phenol had to make the medium sufficiently acidic to prevent coupling, thereby indicating the diazonium ion as the active reagent. The improvement in the yields of diaryl from diazotised nitroanilines when sodium hydroxide is replaced by sodium acetate (cf. Hodgson and Marsden, *J.*, 1940, 208; Hodgson and Foster, *J.*, 1942, 581) is due to the repression (probably complete) of the unreactive nitrosoamine (III) present in the equilibrium system

$$\underset{\text{(I.)}}{NO_2\cdot C_6H_4\cdot N(\equiv N)\,OH} \rightleftharpoons \underset{\text{(II.)}}{NO_2\cdot C_6H_4\cdot N{=}N\cdot OH} \rightleftharpoons \underset{\text{(III.)}}{NO_2\cdot C_6H_4\cdot N(O)\,ONa} + NaOH$$

$$\text{(III.)}\quad NO + H_2O$$

by the production of the simpler system (IV), which then behaves like the analogous very reactive system cited for diazotised 4-nitro-1-naphthylamine (Hodgson, Nicholson, and



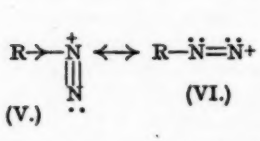
(IV.)

G. Turner, *J.*, 1944, 15). Kühling's observation (*Ber.*, 1895, **28**, 41; 1896, **29**, 165; cf. also Kliegl and Huber, *ibid.*, 1920, **53**, 1641) of the reactivity of an aqueous solution of the sodium salt of diazotised *p*-nitroaniline with toluene, is of course due to the presence of the *p*-nitrobenzenediazonium hydroxide (I) in the equilibrium system above; the fact of its existence has been confirmed by reaction with potassium iodide to form *p*-iodonitrobenzene. The non-reactivity of solid potassium *syn*-diazoate with benzene (Gomberg and Pernert, *loc. cit.*), and the similar non-reactivity of sodium *p*-nitrobenzene-*anti*-diazoate [the nitrosoamine (III) above] with 1-chloro-2 : 4-dinitrobenzene in boiling benzene (Hodgson and Marsden, *J.*, 1945, 207) must be ascribed to the absence of diazonium salt.

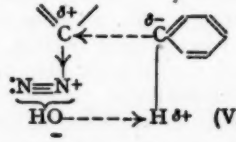
The decrease in yield when other bases are diazotised which do not contain nitro-groups is probably due to the shift in the equilibrium system in favour of the coupling but non-decomposing diazoate, with consequent diminution in quantity of the reactive diazonium acetate. Gomberg's observation that nitro- and chloro-anilines react better in neutral than in alkaline solution is due to the diminution or even suppression of nitrosoamine formation which alkalis promote, with consequent enhancement of the quantity of the reactive diazonium salt; with aniline and the toluidines, alkali will tend to stabilise the diazo–diazonium equilibrium and reduce phenol formation to a minimum.

Some Anomalies of the Free-radical Hypothesis.—Grieve and Hey (*J.*, 1934, 1797) first pointed out that no attention appeared to have been paid to the invariability of the *p*- and/or *o*-substitution irrespective of any directing group present, and they concluded that the substituting agent must be amphoteric in type, *i.e.*, capable of functioning alternatively as if it were a kationoid or an anionoid reagent as occasion demands, and that a mechanism involving the formation and transient existence of free phenyl radicals will provide the requisite interpretation. The paper cited deals only with the phenyl radical, which may be regarded as amphoteric, but in the decompositions with the stabilised diazonium salts of the nitroanilines (Hodgson and Marsden, *J.*, 1940, 208), where the nitrophenyl radicals, if formed, could hardly be regarded as amphoteric or at the best very feebly so, substitution still occurred in the *p*-position with nitrobenzene, and the largest yield recorded (69%) of *pp'*-dinitrodiphenyl was obtained for the reaction of the diazonium salt from *p*-nitroaniline, in which a radical with a strong kationoid bias would be attacking a kationoid *p*-position. Moreover, Grieve and Hey give no reason why these powerful free radicals should not attack the relatively inert *m*-positions in preference to a hostile (kationoid) *p*-position. This problem admits of ready solution when the free-radical hypothesis is discarded for a polar one, since only from this viewpoint can the absence of *s*-diaryls be interpreted; in addition, the invariability of *op*-substitution must also be explained by it.

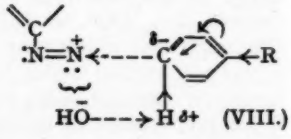
The Polar Theory.—On this hypothesis, the kationoid diazonium ion (stabilised in Hodgson and Marsden's experiments, *J.*, 1940, 208) attacks the anionoid reactant (say benzene) at an anionoid carbon atom (VII), thereby causing its covalent hydrogen to become kationoid and so attracting the anion (usually hydroxyl or acetate) of the diazonium salt. Complete ionisation



(V.) (VI.)



(VII.)



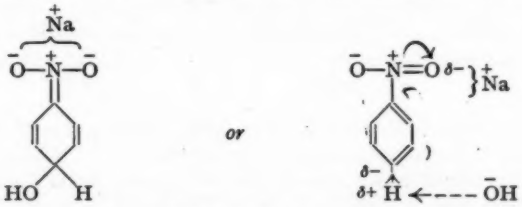
(VIII.)

of the hydrogen with consequent release of the electron enables elimination of nitrogen with consequent formation of diaryl and HX (usually water or acetic acid). *In this reaction free-radical formation never occurs and so the absence of* s*-diaryl is explained.* Azo-formation, which can also occur partially, *e.g.*, with diphenyl, or completely with phenol or naphthol in alkaline, neutral, or slightly acid media, depends on the anionoid character of the significant carbon atom of the second component, which, when sufficiently great, will enable attack by the diazonium ion in resonance structure (VI), so that scission of nitrogen is prevented and an azo-link is established (VIII). For ordinary cases of coupling, therefore, the main driving force is

the formation of water (or the feebly ionised acetic acid), but for a weakly anionoid molecule like benzene, this driving force has to be augmented by that due to elimination of nitrogen [hence attack by the diazonium ion in resonance form (V)]. Both reactions can occur simultaneously, however, to varying extents depending on the anionoid character of the second reactant. In Hirsch's experiments (*loc. cit.*) the anionoid character of the *o*- and *p*-positions in phenol was so reduced by making the reaction medium acidic, with consequent repression of the ionisation of the hydroxyl group, that coupling was prevented [*i.e.*, attack by the diazonium ion in resonance form (VI)] and so diphenyl formation occurred [*i.e.*, attack in resonance form (V) with simultaneous formation of water and molecular nitrogen as driving force]. Moreover, this mechanism is in accord with the kinetic studies of Wistar and Bartlett (*J. Amer. Chem. Soc.*, 1941, **62**, 413), who attribute coupling to the diazonium ion whether in acid or in alkaline solution, nor is it inconsistent with the modified coupling hypothesis of Hodgson (*J. Soc. Dyers and Col.*, 1942, **58**, 228), who postulated the highly polarised diazo-component, $R-N=\overset{\delta+}{N}-\overset{\delta-}{X}$, as the active reagent in ordinary coupling reactions. On this latter viewpoint, coupling depends on the anionoid character of the second component being sufficiently strong to react with the polarised covalent diazo-compound (hydroxide, chloride, sulphate, etc.). If this is impossible, as in benzene, then the diazonium ion in resonance form (V) is necessary to provide the extra driving force by scission of molecular nitrogen. Both reactions can occur simultaneously, however, depending on the anionoid character of the second reactant.

In any event the assumption of free radicals is entirely unnecessary to explain the kinetic results, and if the diazonium ion is responsible for coupling, as claimed by Wistar and Bartlett (*loc. cit.*), surely it must be the active reagent for the case of decreased anionoid character afforded by the Gomberg reaction.

The Anomalous p-*Reactivity of Nitro-hydrocarbons.*—This unexpected reactivity seems to have been one of the main factors which inspired the adoption of a free-radical theory for the Gomberg reaction by Grieve and Hey (*loc. cit.*). It can, however, be attributed to solvent action at the nitro-group, whereby the kationoid character of the *op*-positions is reversed to anionoid. Since *m*-dinitrobenzene and *s*-trinitrobenzene form stable salts with sodium or potassium hydroxide in methyl alcohol, which in the latter case are very stable (cf. Sidgwick, " Organic Chemistry of Nitrogen ", 1937, p. 260), incipient salt formation can reasonably be assumed for nitrobenzene, and either a quinonoid formulation be adopted (cf. Meisenheimer,

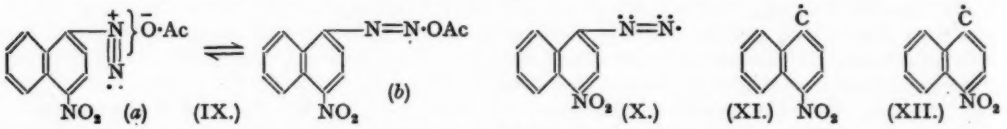


Annalen, 1902, **323**, 205), or, alternatively, the hydroxyl anion can be assumed to be attracted to the partly ionised hydrogen, with similar structures for the corresponding *o*-quinonoid forms. The diazonium ion will then join with the hydroxyl ion in a two-point attack at the $\overset{\delta-}{>}C-\overset{\delta+}{H}$ bond, whereby diphenyl formation will occur. The overwhelming predominant activity of the *p*-position and the absence of *m*-reactivity are thus accounted for, since of the incipient *o*- and *p*-quinonoid structures brought into being by the salt formation, the latter is the more stable (cf. Veselý and Jakeš, *Bull. Soc. chim.*, 1923, **33**, 955, for the relative stabilities of the *p*- and *o*-quinonoid structures). In the more intimate interaction which the sodium acetate–glacial acetic acid medium provides, possibly by hydrogen bonding with the nitro-group, or salt formation, or both, the anionoid activity is developed as above to such an extent that the yield of diaryl increases about sevenfold.

In the case of *o*-nitrotoluene, Grieve and Hey (*loc. cit.*) found that substitution occurred more readily at the *op*-positions with respect to the nitro-group than at the corresponding positions with respect to the methyl group, a fact which illustrates the present argument that the greater tendency to produce ionic quinonoid structures exhibited by the nitro-group over the methyl group has resulted in the greater reactivity at the *op*-positions to the nitro-group.

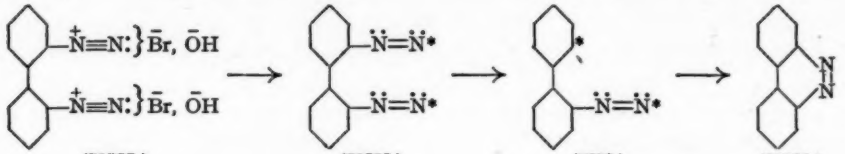
A Partial Analogy with the Gomberg Reaction.—Analogy is to be found in many respects during the gradual decomposition of 4-nitronaphthalene-1-diazonium chloride (or sulphate) by sodium acetate in aqueous solution, and incidentally in a homogeneous medium (Hodgson,

Nicholson, and G. Turner, *J.*, 1944, 15). The decomposition takes several hours to complete, but can be arrested at any time by addition of hydrochloric acid. The precipitated reaction products consist mainly of 4 : 4′-dinitronaphthalene-1′ : 2-azo-1-naphthol, 4 : 4′-dinitro-1 : 1′-azonaphthalene, and 4 : 4′-dinitro-1 : 1′-dinaphthyl, and their formation corresponds with the setting up of the equilibrium (IX, *a*) ⇌ (IX, *b*), after which the following simultaneous reactions occur : (1) Decomposition of (IX, *a*) by anionoid water or by hydroxyl ions in the



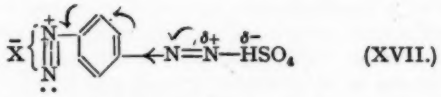
normal manner to form 4-nitro-1-naphthol, which will then couple with (IX, *b*) to form the azo-dye. Decomposition of (IX, *a*) by an oxidation–reduction process, probably facilitated by the equilibrium disturbance necessitated by reaction (1), whereby radicals (X) and (XI) result on the one hand, and irresolvable oxidation products on the other, which are very soluble in acetone. Union of (X) and (XI) affords the azo-compound, while union of two (XI) radicals gives the dinaphthyl. The mechanism of this reaction thus fits in with the scheme adopted by the author for all diazo-decompositions. The outstanding difference from the Gomberg reaction is the formation of *s*-dinaphthyl, and here apparently the 4-nitronaphthyl radical (XII) when formed is sufficiently stabilised by the nitro-group to have a free existence and so enabled to combine with another like radical.

The Closure of the Dibenzopyridazine (*Diphenylazone*) *Ring*.—This reaction takes place either by the action of cuprous bromide (Dobbie, Fox, and Gauge, *J.*, 1911, **99**, 1615) in acid solution, or by that of alkaline sodium arsenite (Sandin and Cairns, *J. Amer. Chem. Soc.*, 1936, **58**, 2019) on tetrazotised 2 : 2′-diaminodiphenyl. The same explanation as that given by H. *et al.* (*loc. cit.*) for the formation of *s*-azo-derivatives in acid solution can hold for both cases, *viz.*, the initial formation of a bisdiazonium compound (XIII), with subsequent transfer of two electrons from the reducing agent to form the di-radical (XIV), partial elimination of nitrogen



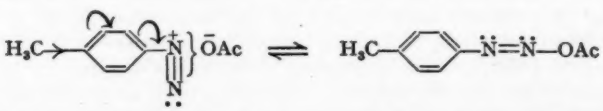
(XV), and consequent closure of the ring to give dibenzopyridazine (XVI). This simple electronic explanation applies to both cases and avoids the difficulty of S. & W., who, while postulating homolytic fission in the alkaline case, have to resort to heterolytic fission and special pleading for the acid case.

Incidentally, it is of interest that where both a diazonium and a covalent diazo-group can exist together as in tetrazotised *p*-phenylenediamine in concentrated sulphuric–phosphoric acid solution (Schoutissen, *J. Amer. Chem. Soc.*, 1933, **55**, 4541) (XVII), the diazo-group can couple in the strong acid solution, *i.e.*, retain its nitrogen, while the diazonium group will



(XVII.)

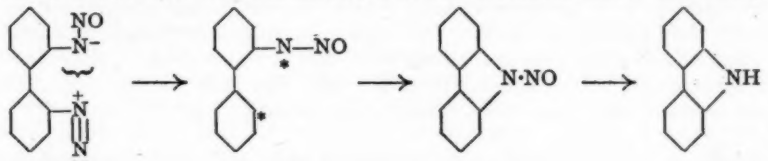
subsequently give the usual reactions of diazonium salts, *i.e.*, it will readily part with its nitrogen. Here, then, is the clue to an explanation of the difference in the decompositions of nitrosoacylaryl- and nitrosoacylalphyl-amines, since the aryl will be more in the diazonium condition



than the alphyl compound owing to the inductive (+ *I*) effect of the alkyl group in the alphyl compound diminishing the positive character of the diazonium group and hence producing a

shift in the diazo–diazonium equilibrium in favour of the diazoacetate : In consequence, the Gomberg reaction will have less driving power than in the case of the nitrosoacylarylamines.

Carbazole Formation in the Acid Dibenzopyridazine Reaction.—The appreciable yield of carbazole obtained in this reaction is not dealt with by S. & W., but whereas an explanation appears to be well-nigh impossible on the free-radical hypothesis, it readily follows from the author's viewpoint, *viz.*, that on tetrazotisation one diazonium group may readily pass into the nitrosoamine form under the influence of the other (cf. the partial analogy in Schoutissen's reaction, where one diazonium group passes into the diazo-form), with initial salt formation (XVIII), whence passage of an electron from the nitrosoamine to the diazonium group causes elimination of nitrogen (XIX), and ring closure (XX) with subsequent hydrolysis produces carbazole (XXI), the yield of which is improved by rise of temperature. An analogous reaction

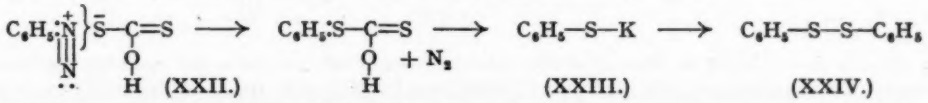


(XVIII.) (XIX.) (XX.) (XXI.)

in which strongly positive diazonium groups are concerned is the formation of 4 : 8 : 4′ : 8′-tetranitro-1 : 1′-dinaphthylamine by the action of cuprous hydroxide on 4 : 8-dinitronaphthalene-1-diazonium sulphate (Hodgson and Crook, *J.*, 1937, 571). It will be recalled that Schoutissen (*J. Amer. Chem. Soc.*, 1933, **55**, 4541) found that a diazonium group was as effective in its electron-attracting influence as two nitro-groups.

The tendency to carbazole formation when tetrazotised 2 : 2′-diaminodiphenyl is decomposed, and the electronic situation necessitated, may well account for the difficulty in carrying out the ordinary Sandmeyer reaction. Incidentally, the main product of the reaction between the above tetrazo-compound and potassium iodide is carbazole (Mascarelli, *Gazzetta*, 1908, **38**, ii, 619), the di-iododiphenyl being formed in small amount only.

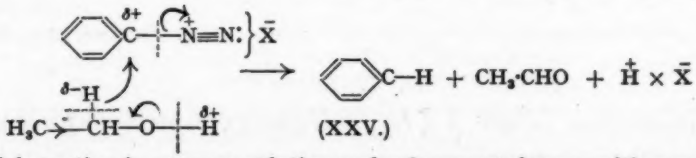
The Decompositions of Benzenediazo-hydroxide in (a) *Carbon Disulphide,* (b) cyclo*Hexane, and* (c) *without Added Solvent* (cf. Waters, *J.*, 1937, 2014).—(*a*) In accord with Leuckardt's classical work (*J. pr. Chem.*, 1890, **41**, 170; Hartley and Smiles, *J.*, 1926, 1824), the reaction can proceed normally *via* a diazonium xanthate (XXII), which by elimination of nitrogen and subsequent hydrolysis gives the mercaptate (XXIII) with subsequent oxidation to the disulphide (XXIV), without recourse to the hypothesis of free radicals :



(XXII.) (XXIII.) (XXIV.)

(*b*) This reaction, which yields benzene, is analogous to the corresponding reduction by ethyl alcohol, where the anionoid CH_2 group in (XXV) supplies the hydrogen as in the attached scheme, since *cyclo*hexane is a ring of anionoid CH_2 groups.

(*c*) In the general scheme put forward by Waters (*J.*, 1942, 266) the homolysis of undissociated diazo-compounds into two free radicals with liberation of nitrogen was regarded as occurring regularly only in non-dissociating solvents (cf. Grieve and Hey, *J.*, 1938, 109), but he stated (*J.*, 1946, 1155) that the production of a trace of benzene in decomposition (*c*) showed



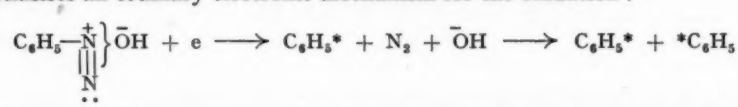
(XXV.)

that radical formation in aqueous solution and subsequent decomposition as $Ar^{*} + H_2O \longrightarrow Ar{-}H + {}^{*}OH$ *is not quite impossible.* This decomposition has been reinvestigated by the author with Dr. E. R. Ward, and nitrobenzene obtained in small yield. We have not been able to detect the trace of benzene mentioned, because nitrobenzene itself gives a positive test by the iodic acid method (Masson and Race, *J.*, 1937, 1718), and *m*-dinitrobenzene on further nitration; in addition, we have obtained aniline by reduction. Consequently, we believe that the trace of benzene recorded was actually nitrobenzene.

In the same paper (*loc. cit.*) the Bart reaction is cited as occurring spontaneously without recourse to any copper derivative as catalyst, the presence of the reducing agent which brings about the reaction being apparently overlooked.

The Reactions of Benzenediazonium Chloride with Solvents and Metals in Absence of Water.—Since Waters (*J.*, 1937, 2010) states that Sir Robert Robinson pointed out that the reactions previously discussed by Waters (*J.*, 1937, 113, 200) could all be considered as typical interactions between covalent diazobenzene chloride and another reagent, any apparent analogy with reactions in aqueous solution should, in the author's opinion, not be unduly stressed.

The Oxidising Reactions of Diazobenzene Hydroxide.—The first example quoted (*J.*, 1937, 2015) is the oxidation of leuco-methylene-blue by *benzenediazonium sulphate*, which, apart from the irony of the situation, indicates a much simpler mechanism than that of free radicals since it is the readiness to be an electron acceptor which gives to the diazonium ion its oxidising properties. All the oxidations (cited in the paper) of diazo-compounds in aqueous solution are due to electron acceptance by diazonium ions, and the fact that diphenyl derivatives are also regular by-products (cf. Schmidt, *Annalen*, 1920, **421**, 159; Bart, *ibid.*, 1922, **429**, 55) emphasises an ordinary electronic mechanism for the oxidation:



Conclusion.—(1) The source of the free radicals in Hey and Waters's hypothesis is given as the undissociated diazo-hydroxide, the amount of which is regarded as considerable, especially near neutrality, in striking contrast to the views of Conant and Tishler ("The Chemistry of Organic Compounds", Macmillan, 1939, p. 382), who consider that the free diazo-hydroxide is only present in very small amount at any time.

(2) The positivity of the carbon atom to which the diazonium group is attached is a determining factor in diazo-decompositions in sulphuric acid with cuprous hydroxide (cf. Hodgson, Leigh, and G. Turner, *loc. cit.*; Hodgson, Birtwell, and Walker, *J.*, 1941, 770). Gradations of positivity are well exemplified as follows: formation of symmetrical azo-compounds (minimum positivity), of dinaphthyls (medium), and replacement by hydrogen (maximum). This viewpoint is much simpler than any which the hypothesis of free radicals could provide.

(3) The formation of diaryl compounds from nitrosoacylarylamines is due to the presence of diazonium salt in the equilibrium scheme:

and there is no evidence to show that the solid nitrosoacylarylamine is not such an equilibrium mixture; on the contrary, the reactions investigated by Hey *et al.* indicate the existence of such a mixture.

(4) S. & W. exclude the reduction of diazotised α- and β-naphthylamine with alkaline sulphite (Lange, D.R.-P., 78,225) because there is no *a priori* evidence (*e.g.*, the isolation of diaryls or of azo-diaryls) that free radicals are concerned. It must be pointed out that the patent refers to reaction in acetic acid solution, and that the mechanism involved has already been adequately discussed on the same lines as heretofore (cf. Hodgson, Nicholson, and G. Turner, *J.*, 1944, 15), and for cases where dinaphthyl formation occurs alongside that of *s*-azo-compounds.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, April 29th*, 1947.]

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86. *Cinnolines. Part XVI.* 4-*Hydroxy*-3-*methylcinnolines.*

By J. R. KENEFORD and J. C. E. SIMPSON.

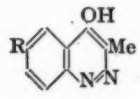
A description is given of the synthesis of a series of Bz-substituted 4-hydroxy-3-methylcinnolines from propiophenone by way of fully authenticated intermediates.

THE recent publications of Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 405, 419) on the preparation of 4-hydroxycinnolines by methods similar to those described in earlier papers of this series (*J.*, 1945, 520, 646) contain an account of the synthesis of 4-hydroxy-3-methylcinnoline

(I; R = H) and its 6-bromo- and 6-nitro-derivative (I; R = Br and NO_2). Experiments which we began several years ago followed closely similar lines, but, in addition, provided unambiguous evidence for the structures of the products.

The nitration of propiophenone to *o*- and *m*-nitropropiophenone has been described by Elson, Gibson, and Johnson (*J.*, 1930, 1128), by Leonard and Boyd (*loc. cit.*), and by Zenitz and Hartung (*ibid.*, 1946, **11**, 444). In our hands, the reaction also yielded a small amount of a weakly acidic *substance* of probable formula $C_9H_8O_4N_2$, which does not appear to be any obvious simple derivative of propiophenone. Reduction of the nitro-ketones to *o*- and *m*-aminopropiophenone proceeded smoothly when tin and stannous chloride, respectively, in hydrochloric acid were used, each method being, apparently, an improvement on previous results (Elson, Gibson, and Johnson, *loc. cit.*; Leonard and Boyd, *loc. cit.*). Some 5-chloro-2-aminopropiophenone was formed by nuclear chlorination during the reduction of *o*-nitropropiophenone, as shown by the fact that diazotisation and cyclisation of (distilled) material produced small amounts of the corresponding chlorohydroxycinnoline in addition to 4-hydroxy-3-methylcinnoline; when, however, *o*-aminopropiophenone regenerated from the *acetyl* derivative was so treated, only 4-hydroxy-3-methylcinnoline was obtained.

Nitration of *o*-acetamidopropiophenone, in our experience, follows the same course as that of *o*-acetamidoacetophenone (*J.*, 1947, 237), and yields both 5-nitro- (II; R = Ac) and (in smaller amount) 3-*nitro*-2-*acetamidopropiophenone* (III; R = Ac). Leonard and Boyd (*loc. cit.*), on the other hand, obtained only a poor yield of a single product, which they correctly assumed to be (II; R = Ac). 5-*Nitro*-2-*aminopropiophenone* (II; R = H), obtained from (II; R = Ac), gave *m*-nitropropiophenone on deamination; and, as the reduction product of 3-*nitro*-2-*aminopropiophenone* (III; R = H) readily condensed with phenanthraquinone to the phenazine (IV), the orientations of both nitroaminopropiophenones are established.



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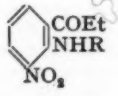

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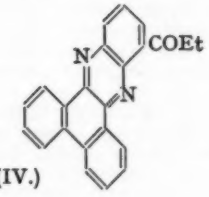

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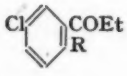

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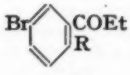

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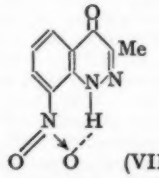

(VII.)

m-Chloro- and *m*-bromo-propiophenone, obtained from *m*-aminopropiophenone, gave on nitration 5-*chloro*- and 5-*bromo*-2-*nitropropiophenone* (V and VI; R = NO_2). Reduction of these compounds yielded 5-*chloro*- and 5-bromo-2-aminopropiophenone (V and VI; R = NH_2); the latter amine is without doubt identical with the substance which Leonard and Boyd (*loc. cit.*) obtained *via* the bromination of *o*-acetamidopropiophenone, and for which they assumed the same structure. The orientations of our products were established by conversion into 5-*chloro*- and 5-*bromo*-2-*benzamidopropiophenone* (V and VI; R = NHBz), identical with the products obtained from (II; R = H) by successive benzoylation and reduction followed by the appropriate Sandmeyer reaction.

Diazotisation of the foregoing *o*-amino-ketones, followed by cyclisation, yielded 4-hydroxy- (I; R = H), 6-*chloro*-4-*hydroxy*- (I; R = Cl), 6-bromo-4-hydroxy- (I; R = Br), 6-nitro-4-hydroxy- (I; R = NO_2), and 8-*nitro*-4-*hydroxy*-3-*methylcinnoline* (VII). 4-Hydroxy- and 6-nitro-4-hydroxy-3-methylcinnoline were readily converted into the corresponding 4-*acetoxy*-derivatives (cf. Schofield and Simpson, *J.*, 1945, 512). The 8-nitro-compound, however, was not attacked by boiling acetic anhydride; in this respect it resembles 8-nitro-4-hydroxycinnoline itself (*J.*, 1947, 237), and is accordingly formulated as (VII). The hydrogen bonding is not, however, sufficiently strong to withstand the action of a mixture of phosphorus pentachloride and oxychloride, which converted (VII) smoothly into the 4-chloro-derivative, from which 8-*nitro*-4-*phenoxy*-3-*methylcinnoline* was prepared. Analogous *derivatives* were also prepared from (I; R = H) and from (I; R = NO_2), the former of which was also converted into 4-*anilino*-3-*methylcinnoline*.

Experimental.

(M. ps. are uncorrected.)

Nitration of Propiophenone.—A mixture of the ketone (60 c.c.) and acetic acid (8 c.c.) was added during ½—¾ hour to nitric acid (300 c.c., *d* 1·5) at −10° to 0°. After a further ½ hour at −5°, the mixture was poured on ice (1200 g.) and the crude solid filtered off (filtrate *A*) and recrystallised from alcohol, giving *m*-nitropropiophenone, m. p. 101—102°. Filtrate *A* was made alkaline with solid sodium carbonate and extracted with ether. The extract was washed with aqueous sodium hydroxide (solution *B*), dried, and evaporated, and the residue combined with the solvent-free material contained in the alcoholic filtrates from the *m*-nitro-ketone. In this way 425 g. of propiophenone gave 298 g. of pure *m*-nitro-ketone and 181 g. of crude *o*-nitropropiophenone (total nitro-ketones, 84%; if the treatment of filtrate *A* is omitted, the yield is 70—75%). Acidification of solution *B* gave a solid which separated from benzene in almost colourless prismatic needles (12 g.), m. p. 158—159° (Found: C, 51·4; H, 3·85; N, 13·2. $C_9H_8O_4N_2$ requires C, 51·9; H, 3·9; N, 13·45%). This *substance* is readily soluble in dilute aqueous sodium hydroxide, but insoluble in aqueous sodium carbonate; it is stable to air in the dark, but it darkens when kept in daylight in an evacuated desiccator, the m. p. falling to *ca.* 150° after a few days.

Preparation of o- *and* m-*Aminopropiophenone.*—The crude *o*-nitro-ketone (520 g.) was reduced with tin and hydrochloric acid exactly as described for *o*-aminoacetophenone (*J.*, 1945, 646), using 25 g. batches; the *o*-aminopropiophenone (332 g., 76%) had b. p. 142—146°/15—17 mm. and crystallised on cooling, but contained some 5-chloro-2-aminopropiophenone, which was readily removed by crystallisation of the acetyl derivative. o-*Acetamidopropiophenone* [crude, 93 g., m. p. 64—70°, from the amine (77·3 g.) and acetic anhydride (150 c.c.) heated for 1 hour at 90—95°] crystallised from ether–ligroin (b. p. 60—80°) in gross colourless prisms, m. p. 73—74° (82 g.) (Found: C, 68·95; H, 6·6. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·85%); Leonard and Boyd (*loc. cit.*) give m. p. 70—71° for unanalysed material.

A solution of *m*-nitropropiophenone (21·6 g.) in warm glacial acetic acid (60 c.c.) was added to a stirred solution of stannous chloride dihydrate (100 g.) in hydrochloric acid (7·5 N, 240 c.c.); after 1 hour at 90—95° the amine (17·3 g., 96%) was isolated as a pale yellow oil (which slowly crystallised) by addition of excess of aqueous sodium hydroxide and extraction with ether. Using iron and acetic acid, Elson, Gibson, and Johnson (*J.*, 1930, 1128) found that the reaction was erratic, but we observed a smooth reaction under the conditions described (*J.*, 1945, 646) for *o*-aminoacetophenone, although the yield was somewhat lower than that given by the stannous chloride method. Acetylation of material obtained by either method gave, quantitatively, m-*acetamidopropiophenone* as stout polyhedra, m. p. 92—93°, from benzene–ligroin (b. p. 40—60°) (Found: C, 69·55; H, 6·55. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·85%); nitration of this under conditions which were successful (*loc. cit.*) with *m*-acetamidoacetophenone gave only resinous material. m-*Acetamidopropiophenone semicarbazone*, colourless needles from aqueous alcohol, had m. p. 196—197° after shrinking at 188° (Found: N, 23·0. $C_{12}H_{16}O_2N_4$ requires N, 22·6%).

m-*Chloropropiophenone and its Derivatives.*—The following compounds were prepared by methods corresponding precisely to those described below for the bromo-compounds. *m*-Chloropropiophenone [29·8 g. (77%) from 34·6 g. of amine] had b. p. 124°/14 mm., m.p. 48—49°; Zenitz and Hartung (*loc. cit.*) give m. p. 45—46°, and yield 73%. 5-*Chloro*-2-*nitropropiophenone* [crude, 12·1 g. (95%), m. p. 64—71°, from 10 g. of chloro-ketone], formed long, colourless, prismatic needles, m. p. 78—78·5°, from alcohol (Found: C, 50·8; H, 3·9. $C_9H_8O_3NCl$ requires C, 50·55; H, 3·8%). 5-*Chloro*-2-*aminopropiophenone* (crude, 98%), pale yellow irregular blades from ligroin (b. p. 60—80°), had m. p. 80—80·5° (Found: N, 7·85. $C_9H_{10}ONCl$ reauires N, 7·6%). 5-*Chloro*-2-*benzamidopropiophenone*, prepared both from the above amine and also from 5-amino-2-benzamidopropiophenone (*q.v.*), separated from alcohol in minute glittering needles, m. p. 125—126° (Found: N, 5·15; Cl, 12·1. $C_{16}H_{14}O_2NCl$ requires N, 4·9; Cl, 12·3%).

m-*Bromopropiophenone.*—A solution of *m*-aminopropiophenone (17 g.) in hydrobromic acid (40 c.c., *d* 1·5) and water (80 c.c.) was diazotised with 20% aqueous sodium nitrite and added during 10 minutes to a solution of cuprous bromide (from 37·5 g. of copper sulphate crystals) in hydrobromic acid (65 c.c., *d* 1·5) and water (35 c.c.). After 1 hour at room temperature, the mixture was kept at 50—60° for 20 minutes. The bromo-ketone, collected with ether, distilled as a heavy sweet-smelling oil at 138—140°/17 mm. (17 g.; 70%) which rapidly crystallised [m. p. 41—42° from ligroin (b. p. 40—60°)] (Found: C, 50·9; H, 4·4. Calc. for C_9H_9OBr: C, 50·7; H, 4·2%). Elson, Gibson, and Johnson (*loc. cit.*) give m. p. 36° (52% yield); Zenitz and Hartung (*loc. cit.*) give m. p. 37·5—40° (44% yield).

5-*Bromo*-2-*nitropropiophenone.*—The bromo-ketone (2 g.) was added during 10 minutes to nitric acid (12 c.c., *d* 1·5) at −5 to −3°. After a further 20 minutes at −3° the solution was poured into ice–water; 5-*bromo*-2-*nitropropiophenone* crystallised from aqueous alcohol in long colourless needles (1·35 g.), m. p. 74·5—76° (Found: C, 42·0; H, 3·2. $C_9H_8O_3NBr$ requires C, 41·9; H, 3·1%).

5-*Bromo*-2-*aminopropiophenone.*—The foregoing compound (1 g.) was reduced with acetic acid (6 c.c.), water (6 c.c.), and iron filings (1·5 g.) by the method previously described (*J.*, 1945, 646). The amine, isolated by means of ether, formed slender yellow needles (0·7 g.), m. p. 79—80°, from aqueous alcohol (Found: C, 47·4; H, 4·6. Calc. for $C_9H_{10}ONBr$: C, 47·4; H, 4·4%). Leonard and Boyd (*loc. cit.*) give m. p. 79—80°.

Nitration of o-*Acetamidopropiophenone.*—The acetyl derivative (53·4 g.) was added during 30 minutes to a stirred mixture (325 c.c.) of nitric acid (*d* 1·48) and concentrated sulphuric acid [5 : 1 v/v] at −13° to −5°. After a further 15 minutes, the solution was poured on ice (2 kg.); the crude 5-nitro-2-acetamidopropiophenone so obtained (53·5 g., 80%, m. p. 137—138°) crystallised from alcohol in long, soft colourless needles, m. p. 145—145·5° (Found: C, 56·2; H, 4·8; N, 11·5. Calc. for $C_{11}H_{12}O_4N_2$: C, 55·9; H, 5·1; N, 11·9%); Leonard and Boyd (*loc. cit.*) give m. p. 144—145° (40% yield). The aqueous acid mother liquor was basified with solid sodium carbonate, the solid (*A*) filtered off, and the filtrate extracted with ether; the extract was washed dried, and concentrated, and the residue combined with (*A*) and crystallised from alcohol, yielding crude 3-*nitro*-2-*acetamidopropiophenone* (12·5 g., 19%), m. p. 100—103°;

the pure compound formed almost colourless prismatic needles, m. p. 109—110°, from alcohol (Found: C, 56·1; H, 5·1; N, 12·1. $C_{11}H_{12}O_4N_2$ requires C, 55·9; H, 5·1; N, 11·9%).

5-Nitro-2-aminopropiophenone.—A mixture of the acetamido-compound (53·5 g.) and hydrochloric acid (5N, 320 c.c.) was refluxed for ½ hour, cooled, made alkaline with ammonia, and the crude amine (43·3 g., m. p. 120—122°) recrystallised from alcohol; *5-nitro-2-aminopropiophenone* formed spherical aggregates of yellow needles, m. p. 129—130° (Found: N, 14·8. $C_9H_{10}O_3N_2$ requires N, 14·4%). A hot solution of the amine (2 g.) in concentrated hydrochloric acid (25 c.c.) was cooled rapidly and treated with a solution of sodium nitrite (0·8 g.) in water (2 c.c.). Hypophosphorous acid (30%, 35 c.c.) was added at 0° during 10 minutes to the filtered solution with stirring, and the whole was left at 0° for 24 hours. The solid was then collected (0·55 g., m. p. 96—100°) and sublimed at 70—80°/0·5 mm., yielding *m*-nitropropiophenone, m. p. and mixed m. p. 100—102°.

5-Bromo-2-benzamidopropiophenone.—(*a*) Benzoylation (pyridine and benzoyl chloride) of 5-nitro-2-aminopropiophenone (1·5 g.) gave *5-nitro-2-benzamidopropiophenone* (2·05 g.) as fine colourless needles, m. p. 185·5—186°, from benzene (Found: C, 64·7; H, 4·8. $C_{16}H_{14}O_4N_2$ requires C, 64·4; H, 4·7%), which (1·9 g.) was reduced at 90—95° with iron powder (4 g.), acetic acid (25 c.c.), and water (24 c.c.) (cf. *J.*, 1945, 646) to *5-amino-2-benzamidopropiophenone*, greenish-yellow hair-like needles, m. p. 178·5—179·5°, from benzene (Found: C, 71·5; H, 6·1. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0%). This amine (1 g.) was warmed with a mixture of hydrobromic acid (5 c.c., *d* 1·5) and water (20 c.c.), and the cold suspension diazotised with 5% aqueous sodium nitrite (7·5 c.c.) and added to a solution of cuprous bromide (from 2·4 g. of copper sulphate) in hydrobromic acid (7·5 c.c., *d* 1·5). After being kept at 60° for ½ hour, the product, isolated with ether, was crystallised repeatedly from alcohol and finally from ligroin (b. p. 60—80°), giving the bromobenzamido-compound (poor yield), m. p. 115—116° alone and in admixture with the sample described below.

(*b*) Benzoylation of 5-bromo-2-aminopropiophenone (prepared from *m*-bromopropiophenone) and crystallisation of the product from ligroin (b. p. 60—80°) yielded *5-bromo-2-benzamidopropiophenone* as long, lemon-yellow needles, m. p. 117—118° (Found: C, 58·15; H, 4·45. $C_{16}H_{14}O_2NBr$ requires C, 57·85; H, 4·25%).

3-Nitro-2-aminopropiophenone.—Prepared similarly to the above isomer, this *amine* (8·9 g. from 12·5 g. crystallised from alcohol in fine, deep orange needles, m. p. 90—91° (Found: N, 14·0. $C_9H_{10}O_3N_2$ requires N, 14·4%). Reduction of this compound (0·5 g.) with iron powder (0·8 g.), acetic acid (4 c.c.), and water (4 c.c.) (cf. *J.*, 1945, 646) gave the diamine (0·45 g.) as a slowly crystallising oil; this was converte dwith phenanthraquinone (0·5 g.) in alcohol (75 c.c.) into the *phenazine*, which separated from acetic acid in long, almost colourless needles, m. p. 181—182° (Found: C, 82·3; H, 4·9. $C_{23}H_{16}ON_2$ requires C, 82·1; H, 4·8%).

4-Hydroxy-3-methylcinnoline.—Pure *o*-acetamidopropiophenone (60 g.) and hydrochloric acid (5N, 300 c.c.) were refluxed for ½ hour; the resultant amine (45·5 g.) in concentrated hydrochloric acid (1·2 l.) was treated with cold sodium nitrite (23 g.) in water (30 c.c.) and filtered; concentrated hydrochloric acid (4 l.) was added, and the whole kept at 60° for 4 hours and then evaporated to a small volume (reduced pressure). Addition of excess of saturated aqueous sodium acetate precipitated almost pure 4-hydroxy-3-methylcinnoline (40·7 g.; 83%), which separated from 50% aqueous alcohol in slender silvery needles, m. p. 241—242° (Found: C, 67·3; H, 5·1; N, 17·3. Calc. for $C_9H_8ON_2$: C, 67·45; H, 5·05; N, 17·5%). Leonard and Boyd (*loc. cit.*) give m. p. 248—249° (corr.); yield, 18%. The use of *o*-aminopropiophenone (5 g.), purified by distillation but not by acetylation, in an otherwise similar experiment furnished, as the least soluble fraction, 6-chloro-4-hydroxy-3-methylcinnoline (yield of almost pure material, 0·23 g.), having m. p. 325—326° alone and in admixture with authentic material (*q.v.*), and giving a positive Beilstein test; the filtrates gave 4-hydroxy-3-methylcinnoline (2·65 g.). *4-Acetoxy-3-methylcinnoline*, prepared from the hydroxy-compound and acetic anhydride (6 parts) by refluxing for ½ hour, formed colourless prismatic needles, m. p. 117—117·5°, from alcohol (yield, almost quantitative) (Found: C, 65·4; H, 4·95; N, 14·2. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·85%).

6-Nitro-4-hydroxy-3-methylcinnoline.—A hot solution of 5-nitro-2-aminopropiophenone (34·5 g.) in concentrated hydrochloric acid (750 c.c.) was quickly cooled, diazotised with 50% aqueous sodium nitrite (30 c.c.), kept at 90° for 3 hours, and the solid collected and washed (30 g.). After dissolution in aqueous sodium hydroxide, precipitation with acetic acid, and crystallisation (acetic acid), 6-nitro-4-hydroxy-3-methylcinnoline formed brown irregular blades, which darkened at 340° but did not melt at 360° (Found: C, 53·1; H, 3·5; N, 20·3. Calc. for $C_9H_7O_3N_3$: C, 52·65; H, 3·45; N, 20·5%). Leonard and Boyd (*loc. cit.*) give m. p. >350° (yield, 65%). *6-Nitro-4-acetoxy-3-methylcinnoline*, from the hydroxy-compound and acetic anhydride (10 parts) under reflux for 1 hour, crystallised from benzene in colourless, fern-like blades, m. p. 194—194·5° (Found: C, 53·55; H, 3·6; N, 16·65. $C_{11}H_9O_4N_3$ requires C, 53·4; H, 3·7; N, 17·0%).

8-Nitro-4-hydroxy-3-methylcinnoline.—A solution of 3-nitro-2-aminopropiophenone (11·05 g.) in acetic acid (120 c.c.) and sulphuric acid (85%, v/v; 40 c.c.) was treated with powdered sodium nitrite (4·3 g.) during ½ hour with stirring; after a further 3 hours at 0° and 9 hours at 65—70°, the mixture was poured into water (1 l.) and the solid collected, washed, and dried (11·2 g., m. p. 225—228°). Crystallisation from acetic acid gave *8-nitro-4-hydroxy-3-methylcinnoline* as lustrous, yellow, irregular plates, m. p. 238—239° (Found: C, 52·3; H, 3·7; N, 20·2. $C_9H_7O_3N_3$ requires C, 52·65; H, 3·45; N, 20·5%). Recovery was quantitative after the compound had been refluxed for 1 hour with acetic anhydride (12 parts).

6-Chloro-4-hydroxy-3-methylcinnoline.—Prepared as for the bromo-analogue (*q.v.*), this compound [2·45 g., from the amine (2·45 g.), hydrochloric acid (5N, 24 c.c.), and aqueous sodium nitrite (11%, 10 c.c.)] crystallised from acetic acid in colourless micro-needles, m. p. 328—329° (Found: C, 55·3; H, 4·2; N, 14·2. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·65; N, 14·4%).

6-Bromo-4-hydroxy-3-methylcinnoline.—The suspension of hydrochloride formed from 5-bromo-2-aminopropiophenone (0·5 g.) and 2N-hydrochloric acid (6 c.c.) was treated with aqueous sodium nitrite (10%, 2 c.c.) and heated on the steam-bath for 40 minutes. The cinnoline, easily soluble in cold aqueous

sodium hydroxide, and sparingly in hot alcohol and acetic acid, crystallised from acetic acid in small, soft, colourless needles, m. p. 331—332° (0·3 g.) (Found: C, 44·45; H, 2·95; N, 12·15. Calc. for $C_9H_7ON_2Br$: C, 45·15; H, 2·9; N, 11·7%). Leonard and Boyd (*loc. cit.*) give m. p. 326—327°.

Preparation of 4-Phenoxy-3-methylcinnolines.—The requisite 4-chloro-compounds were prepared by heating a mixture of the hydroxy-compound (5 parts), phosphorus pentachloride (9—13 parts), and phosphorus oxychloride (12—18 parts) for 1 hour on the steam-bath. 4-Chloro-3-methylcinnoline and its 8-nitro-derivative were isolated by ether or chloroform extraction from an alkaline medium as described for other 4-chlorocinnolines (*J.*, 1947, 917) and had m. p. 99—100° (colourless tetrahedra, stable in air for some days but melting over a wide range after 3 months) and 180—181° (yellow prisms) respectively; 4-chloro-6-nitro-3-methylcinnoline (yellow needles, m. p. 146—147°) was usually isolated by precipitation with ligroin from the reaction mixture. A solution in ether (*ca.* 50 c.c.) of the chloro-compound from 4-hydroxy-3-methylcinnoline (10·2 g.) was added to one of potassium hydroxide (3·6 g.) in phenol (36 g.), the ether removed, and the residue heated at 95° for 1 hour. Dilution with water, basification, extraction with ether, and crystallisation from ligroin (b. p. 60—80°) gave *4-phenoxy-3-methylcinnoline* (12·6 g.; 84% based on hydroxy-compound) as colourless prismatic needles, m. p. 78—79°, very soluble in alcohol (Found: C, 76·3; H, 5·2; N, 12·0. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·1; N, 11·85%). The chloro-compound from 6-nitro-4-hydroxy-3-methylcinnoline (25 g.) was added to a mixture of phenol (80 g.) and powdered ammonium carbonate (60 g.) (cf. following paper); after the initial reaction had subsided, the mixture was kept at 90—95° for 1 hour, and the product was isolated as above. Digestion with a little warm 20% aqueous acetic acid (to remove a trace of 6-nitro-4-amino-3-methylcinnoline; see following paper) and crystallisation from alcohol gave *6-nitro-4-phenoxy-3-methylcinnoline* (13·6 g.; 40% based on hydroxy-compound) as long, yellow, striated blades, m. p. 129—130° (Found: C, 64·15; H, 3·8; N, 14·95. $C_{15}H_{11}O_3N_3$ requires C, 64·0; H, 3·95; N, 14·95%). *8-Nitro-4-phenoxy-3-methylcinnoline* (6·15 g.), prepared similarly from the chloro-compound (8·05 g.), phenol (35 g.), and powdered ammonium carbonate (25 g.), crystallised from benzene–ligroin (b. p. 60—80°) in pale yellow prismatic needles, m. p. 137·5—138° (Found: C, 64·5; H, 4·05; N, 15·15. $C_{15}H_{11}O_3N_3$ requires C, 64·0; H, 3·95; N, 14·95%).

4-Anilino-3-methylcinnoline.—Hydrochloric acid (2N; 2 drops) was added to a warm solution of 4-chloro-3-methylcinnoline (0·5 g.) and aniline (0·25 g.) in 50% aqueous acetone (6 c.c.). The solution was refluxed for 25 minutes, cooled, and basified (ammonia), and the precipitated *4-anilino-3-methylcinnoline* (0·63 g., m. p. 215—216°) recrystallised from alcohol, from which it formed bright yellow prismatic needles, m. p. 217—218° (Found: C, 77·0; H, 5·6. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·6%).

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DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

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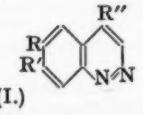
87. *Cinnolines. Part XVII. A Simple Method for the Preparation of 4-Aminocinnolines.*

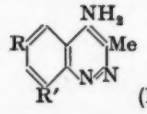
By J. R. KENEFORD, K. SCHOFIELD, and J. C. E. SIMPSON.

4-Aminocinnolines are readily prepared in good yield by reaction between molten ammonium acetate and the corresponding phenoxy-compounds.

VARIOUS problems connected with our studies in the cinnoline field made it necessary to devise a simple, general, and, if possible, inexpensive method for preparing 4-aminocinnolines. Initial experiments in this direction were carried out with 4-chlorocinnoline (I; R = R′ = H, R″ = Cl), and the experience gained in attempting to condense this substance directly with dialkylaminoalkylamines (Simpson and Schofield, *Nature*, 1946, **157**, 439; Keneford and Simpson, *J.*, 1947, 917) indicated that high-temperature reactions would be unlikely to be successful. Treatment of (I; R = R′ = H, R″ = Cl) with aqueous-alcoholic ammonia under pressure at 100—120° gave unchanged material and a *substance*, m. p. 237°, which from analysis



(I.)



(II.)

appeared to be a hydrated aminohydroxycinnoline. The failure of the highly labile 4-chlorocinnoline (examples of the reactivity of this compound are given in the Experimental) to react completely under these conditions is in line with recent findings regarding the stability under mild alkaline conditions of chloro-heterocyclic compounds possessing an iminochloride, or

vinylogous iminochloride, structure (cf. Dobson and Kermack, *J.*, 1946, 150; Curd and Rose, *J.*, 1946, 363; Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2112). The chloro-compound did not react with liquid ammonia at atmospheric pressure or with potassium phthalimide in boiling methyl ethyl ketone in presence of potassium carbonate.

On the other hand, 4-chlorocinnolines in general are readily converted into 4-phenoxycinnolines, which are likewise reactive (see Experimental), and which, further, also condense smoothly with dialkylaminoalkylamines (Keneford and Simpson, *loc. cit.*). The conversion of 4-chloroquinaldines into 4-aminoquinaldines by means of ammonia and phenol at 180° has been described by Backeberg and Marais (*J.*, 1942, 381), and G.P. 708,116 (*Chem. Abs.*, 1943, **37**, 5084) claims the conversion of 4-alkoxy- into 4-amino-quinolines by reaction with ammonium salts and ammonia. It therefore seemed worth while to investigate the reaction between an ammonium salt and 4-phenoxycinnolines, and it was found that, on addition of the latter to molten ammonium acetate, rapid reaction occurred with production of the corresponding 4-aminocinnolines. In this way 4-*amino-* (I; R = R′ = H, R″ = NH_2), 6-*chloro*-4-*amino-* (I; R = Cl, R′ = H, R″ = NH_2), 7-*chloro*-4-*amino-* (I; R = H, R′ = Cl, R″ = NH_2), and 6-*nitro*-4-*amino-cinnoline* (I; R = NO_2, R′ = H, R″ = NH_2), and also 6-*nitro-* (II; R = NO_2, R′ = H) and 8-*nitro*-4-*amino*-3-*methylcinnoline* (II; R = H, R′ = NO_2) were readily prepared. The amines had marked basic properties, but could be precipitated from acid solution by ammonia; they were readily acetylated. Formation of the nitroamines was accompanied by some hydrolysis of the phenoxy- to the hydroxy-compound.

We have also found that this method of preparation of amino-compounds from reactive chloro-compounds can be applied to the quinazoline and quinoline series; examples of these applications will be published in due course.

Experimental.

(M. ps. are uncorrected.)

Reaction of 4-*Chlorocinnoline with Ammonia.*—The chloro-compound (1 g.) was heated with alcohol (4 c.c.) and ammonia solution (4 c.c., *d* 0·88) in a sealed tube at 100° for 2½ hours. Concentration of the solution under reduced pressure gave a solid which, recrystallised from alcohol, yielded light coppery needles of the *product*, m. p. 238—239° (Found: C, 55·35; H, 4·85; N, 24·5. $C_8H_7ON_3,\frac{3}{2}H_2O$ requires C, 55·5; H, 4·8; N, 24·3%). Addition of sodium hydroxide to the filtrates and extraction with ether gave unchanged 4-chlorocinnoline, identified by its positive Beilstein reaction and by recrystallisation from hot water, which converted it into 4-hydroxycinnoline, m. p. and mixed m. p. 230°. Unchanged chlorocinnoline was still present after the reaction time had been increased to 8 hours. In another experiment, the temperature was raised from 20° to 120° during 2½ hours; at this point the product was worked up, and yielded unchanged chloro-compound as sole isolable product [identified as 4-acetoxycinnoline, m. p. and mixed m. p. 124—126° (*J.*, 1945, 512), by short refluxing with acetic anhydride].

Reactions of 4-*Phenoxycinnoline.*—(*a*) The compound (50 mg.) was refluxed for 5 hours in alcohol (0·6 c.c.). Evaporation of the solvent and digestion with ether left crude 4-hydroxycinnoline, m. p. 212—216°, not depressed by admixture with authentic material.

(*b*) The compound (50 mg.) was refluxed for ¾ hour with acetic anhydride (0·5 c.c.). Removal of solvent under reduced pressure and crystallisation from alcohol gave 4-acetoxycinnoline, m. p. 122—124° (124—126° when mixed with an authentic sample).

6-*Nitro*-4-*phenoxycinnoline.*—Application to 4-chloro-6-nitrocinnoline of the phenoxylation method previously described (*J.*, 1947, 917) gave much 6-nitro-4-hydroxycinnoline and only a poor yield of phenoxy-compound; the following conditions were therefore used. 6-Nitro-4-hydroxycinnoline (15 g.), phosphorus pentachloride (20 g.), and phosphorus oxychloride (45 c.c.) were heated on the steam-bath for 1 hour. The mixture was cooled, ligroin (b. p. 40—60°) was added, and the heavy granular solid washed several times by decantation with more ligroin (b. p. 40—60°). Phenol (50 g.) was immediately added, followed by powdered ammonium carbonate (20 g.). The mixture was warmed very slightly to start the reaction and then left for 10 minutes, after which it was heated on the steam-bath for ½ hour. (If the mixture developed an acid reaction—indicated by the appearance of a deep red colour—a little more ammonium carbonate was added until the mass acquired a brown colour; failure to do this resulted in extensive hydrolysis to the hydroxycinnoline.) The mass was then poured into dilute aqueous sodium hydroxide and the oily solid collected. This was suspended in warm water, sodium hydroxide was added until the solution reacted alkaline to litmus, and the granular solid was filtered off, washed, and purified by digestion with hot alcohol (150 c.c.), yielding 6-*nitro*-4-*phenoxycinnoline* (65% yield), m. p. 190—191°. The substance formed yellow blades from alcohol, and silky yellow needles from benzene (Found: C, 63·0; H, 3·6. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4%).

Preparation of 4-*Aminocinnolines.*—The phenoxy-compound (1 part) was added in one portion to ammonium acetate (6 parts) which had been heated to *ca.* 180° (bath temp.) and then allowed to cool to 160°. The temperature was raised during 5 minutes to *ca.* 210° or until a reaction set in (smell of phenol), and maintained at 210—220° until completion of the reaction (usually about 10 minutes; this was in general easily ascertained by the formation of a clear yellow or brown solution). When cold, the melt was diluted with water, the solid collected, and the filtrate basified with ammonia and filtered, and the two crops of solid were combined and digested with a little 30—40% aqueous acetic acid. Filtration and basification gave the amine, which usually separated in almost pure condition.

4-Aminocinnoline (yield, 85%) separated from water in pale yellow leaflets, m. p. 212—213° (Found: C, 65·5; H, 5·1; N, 29·2. $C_8H_7N_3$ requires C, 66·2; H, 4·9; N, 28·9%), and as a hydrate, m. p. 152—154°; each form when refluxed with acetic anhydride gave *4-acetamidocinnoline*, which formed fine lustrous needles, m. p. 272—273°, from alcohol (Found: C, 64·6; H, 4·9; N, 22·5. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·9; N, 22·45%). *6-Chloro-4-aminocinnoline* (85% yield) crystallised from alcohol in small, faintly yellow parallelepipeds, m. p. 277—278° (Found: C, 50·5; H, 3·75; N, 22·4. $C_8H_6N_3Cl,\frac{1}{2}H_2O$ requires C, 50·9; H, 3·75; N, 22·3%). *7-Chloro-4-aminocinnoline* (yield, 95%), pale yellow rods from alcohol, had m. p. 209—210° (Found: C, 51·5; H, 3·8; N, 22·5. $C_8H_6N_3Cl,\frac{1}{2}H_2O$ requires C, 50·9; H, 3·75; N, 22·3%). *6-Nitro-4-aminocinnoline* (yield, 75%) crystallised from a large volume of water in bright yellow needles, m. p. 288—289° (decomp.) (sometimes in small brown prisms) (Found: C, 48·75; H, 3·45; N, 28·4. $C_8H_6O_2N_4,\frac{1}{2}H_2O$ requires C, 48·2; H, 3·5; N, 28·15%); the *acetyl* derivative, m. p. 232—233°, formed ochre-coloured brittle prisms from ethyl acetate (Found: C, 51·9; H, 3·5; N, 24·0. $C_{10}H_8O_3N_4$ requires C, 51·7; H, 3·45; N, 24·1%). *6-Nitro-4-amino-3-methylcinnoline* formed small rust-coloured needles from alcohol, decomposing at 320° without melting (Found: C, 52·85; H, 4·45; N, 27·0. $C_9H_8O_2N_4$ requires C, 52·9; H, 4·0; N, 27·45%). The yield of amine was only 55%, but 40% of 6-nitro-4-hydroxy-3-methylcinnoline was recovered. *8-Nitro-4-amino-3-methylcinnoline* (yield, 45%, together with 55% of recovered hydroxycinnoline) crystallised from alcohol in orange hair-like needles, m. p. 283—285° (decomp.) (Found: C, 52·75; H, 4·1; N, 27·3. $C_9H_8O_2N_4$ requires C, 52·9; H, 4·0; N, 27·45%); the *acetyl* derivative, m. p. 177—178°, separated from alcohol in yellow striated plates (Found: C, 54·1; H, 4·15. $C_{11}H_{10}O_3N_4$ requires C, 53·65; H, 4·1%).

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DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM.
WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

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88. *The Chemistry of Simple Heterocyclic Systems. Part I. Reactions of 6- and 7-Nitro-4-hydroxyquinazoline and their Derivatives.*

By J. S. MORLEY and J. C. E. SIMPSON.

The preparation is described of 6- and *7-nitro-4-amino-*, *-4-acetamido-*, *-4-phenoxy-*, and *-4-anilino-quinazoline*, starting from the appropriate hydroxy-compounds (I and II; R = OH), the properties of which are briefly compared with those of 6-nitro-4-hydroxycinnoline (III).

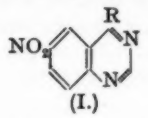
Conversion of the 4-anilino-isomers into stable quaternary *salts* proceeds normally, but with the 4-phenoxy- and 4-acetamido-compounds the reaction leads to fission of the 4-substituents and to production of 6- and *7-nitro-1-methyl-4-quinazolone*, the constitutions of which have been proved by a study of their facile alkaline hydrolysis. 6-Nitro-3-methyl-4-quinazolone and its 7-nitro-*isomer* are similarly hydrolysed and oriented, and a common mechanism is proposed for these alkaline hydrolyses and those of the -4-amino- to the -4-hydroxy-quinazolines; according to this mechanism, the quinazolones and aminoquinazolines are regarded as, respectively, cyclic and semi-cyclic amidines, and the initial step in the hydrolyses is an attack on the amidine double bond.

Reference is also made to the reactivity of the 4-substituted quinazolinium salts, and to the probable non-identity of the sites of substitutive alkylation and of proton-acceptance in 4-hydroxyquinazolines; the former is N^3, and it is concluded tentatively that the latter is N^1.

THE present communication deals with reactions of 6- and 7-nitro-4-hydroxyquinazoline (I and II; R = OH) and their derivatives. The chemistry of these hydroxy-compounds has received little attention despite the fact that they are easily accessible and have been known for many years. The 7-nitro-derivative was first prepared from 4-nitroanthranilic acid by the Niementowski reaction (Bogert and Klaber, *J. Amer. Chem. Soc.*, 1908, **30**, 807); (I; R = OH) was prepared similarly [Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2052; Magidson and Golovchinskaya, *J. Gen. Chem. Russia*, 1938, **8**, 1797 (*Chem. Abs.*, 1939, **33**, 4993)], and also by nitration of 4-hydroxyquinazoline (Bogert and Geiger, *J. Amer. Chem. Soc.*, 1912, **34**, 524). The amine obtained by reduction of (I; R = OH) has been described (Bogert and Geiger, *loc. cit.*; Magidson and Golovchinskaya, *loc. cit.*), and the chloro-compounds (I and II; R = Cl) have also been prepared [U.S.P. 1,880,447 (*Chem. Abs.*, 1933, **27**, 998); Magidson and Golovchinskaya, *loc. cit.*].

The compounds (I and II; R = OH) show important qualitative differences from 6-nitro-4-hydroxycinnoline (III). Thus the hydroxyquinazolines failed to react with acetic anhydride under conditions which result in quantitative acetylation of (III) and other 4-hydroxycinnolines (*J.*, 1945, 512; 1946, 1035; this vol., p. 354); replacement of the hydroxyl group by chlorine also occurs less readily with (I and II; R = OH) than with (III). Again, (I and II; R = OH)

have slight basic properties in addition to their acidic nature, whereas (III) is devoid of basic character. Furthermore, alkylation of (III) with methyl sulphate is notably different from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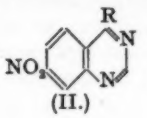
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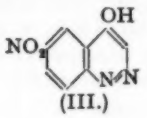
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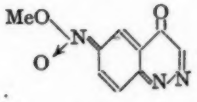
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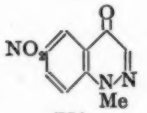
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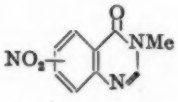

(VI.)

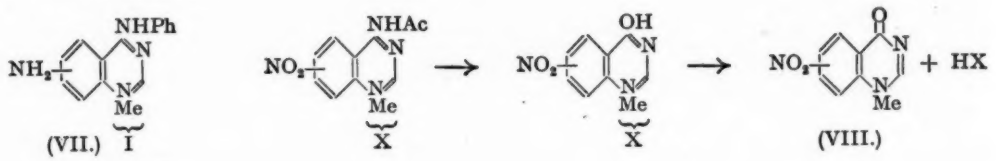
that of (I and II; R = OH); (III) gives a mixture of (IV) and (V) (Schofield and Simpson, *J.*, 1945, 512), but, as is shown later, (I and II; R = OH) give as sole isolable products the corresponding 3-methyl-4-quinazolones (as VI).

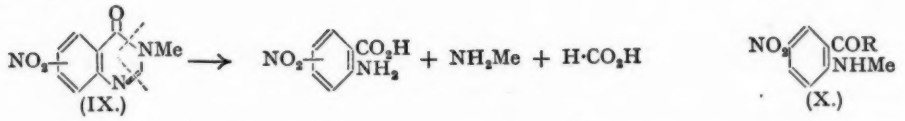
Interaction of the chloronitroquinazolines (I and II; R = Cl) with phenol and solid potassium hydroxide gave 6- and *7-nitro-4-phenoxyquinazoline* (I and II; R = OPh) in moderate yield. The use of ammonium carbonate instead of potassium hydroxide gave the same compounds mixed with 6- and *7-nitro-4-aminoquinazoline* (I and II; R = NH_2), and in the reaction with (I; R = Cl) the 4-aminoquinazoline was the main product under these conditions. On the other hand, the phenol–ammonium carbonate method, which is the standard procedure for making 5-amino- from 5-chloro-acridines (cf. Albert and Gledhill, *J. Soc. Chem. Ind.*, 1942, **61**, 159), gives phenoxy-compound and little or no amino-derivative when applied to nitro-4-chlorocinnolines (this vol., pp. 356, 358). The amines (I and II; R = NH_2) were also prepared easily and in good yield by the method described elsewhere (this vol., p. 358) of fusing the phenoxycompounds with ammonium acetate, and we also found that 6- and 7-nitro-4-aminoquinazoline can be obtained (the 6- more readily than the 7-isomer) from the chloro-compounds and cold ammonia solution (cf. Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2112). The nitro-4-aminoquinazolines, like 4-aminocinnolines (this vol., p. 358), are easily acetylated, but differ from the latter compounds in being readily hydrolysed to the 4-hydroxy-compounds in acid and in alkaline solution. The acid hydrolysis of various 4-alkylaminoquinazolines is mentioned by Tomisek and Christensen (*loc. cit.*).

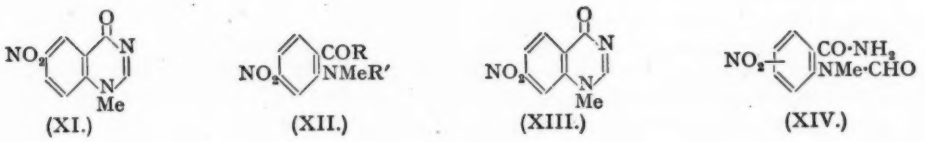
One of the objects of this work was the preparation of quaternary salts of 6- and 7-amino-4-substituted quinazolines and the determination of the site of quaternary salt formation. 4-Aminoquinoline forms quaternary salts on the ring nitrogen (Claus and Frobenius, *J. pr. Chem.*, 1897, **56**, 181, and confirmed in this laboratory), and the same is true of 5-aminoacridine (Albert and Ritchie, *J.*, 1943, 458) and of 6-chloro-4-aminocinnoline (and probably other 4-aminocinnolines) (*J.*, 1947, 1653). However, no well-defined product resulted when 7-nitro-4-aminoquinazoline was refluxed with methyl iodide in alcohol, and it appeared that protection of the 4-amino-group was a prerequisite to effective quaternary salt formation on the ring nitrogen. To this end, (I and II; R = Cl) were condensed with aniline in slightly acid aqueous acetone (cf. Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370), and the resultant 6- and *7-nitro-4-anilinoquinazoline* (I and II; R = NHPh) were converted into quinazolinium *salts* by means of methyl *p*-toluenesulphonate. Conversion of these salts into the *iodides*, followed by reduction, yielded 6- and *7-amino-4-anilino-1-methylquinazolinium iodide* (as VII). 6- and *7-Nitro-4-acetamidoquinazoline* (I and II; R = NHAc) were also smoothly converted into quinazolinium salts with methyl *p*-toluenesulphonate, but, as might be expected in view of the hydrolysis, referred to above, of (I and II; R = NH_2) to (I and II; R = OH), the products obtained, after treatment of the original reaction products with hot acid, were *compounds*, m.p. 271° and 219°, which had the composition of nitromethylquinazolones, removal of the acetamido-group having occurred during either the original reaction or the subsequent working-up. Smooth reactions were likewise observed between methyl *p*-toluenesulphonate and the phenoxy-compounds (I and II; R = OPh), but phenol was eliminated in each case, and the products isolated were the *p-toluenesulphonates* of the same nitromethylquinazolones, m. p. 271° and 219°. These *p*-toluenesulphonates were authenticated by liberation of the quinazolone bases (the salt from 6-nitro-4-phenoxyquinazoline was rapidly hydrolysed in aqueous solution, but the 7-nitro-isomer was more stable), and by the preparation of the salts from the bases and *p*-toluenesulphonic acid.

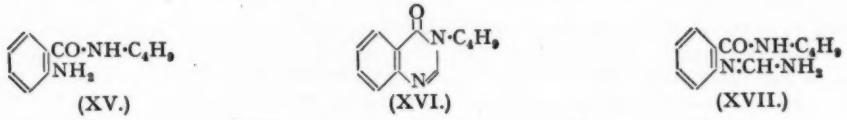
It is clear that the formation of these quinazolone bases from the acetamido- and phenoxy-

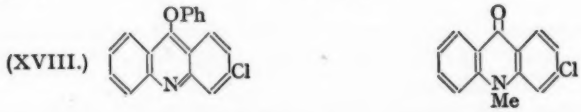
compounds involves an initial quaternary salt formation, followed by hydrolysis either *in situ* (phenoxy-compounds) or possibly at a later stage (acetamido-compounds), as outlined in the formulæ below. The resultant quinazolone bases could conceivably be either the 1-methyl compounds (as VIII) or the 3-methyl isomers; it thus followed that the elucidation of the structures of the compounds, m. p. 271° and 219°, would disclose the point of quaternary salt formation, and hence the basic centre, of the parent quinazolines. This question was settled in the following way.











First, the preparation of 6- and 7-*nitro*-4-*methoxyquinazoline* (I and II; R = OMe) by reaction between methanolic sodium methoxide and the respective chloro-compounds eliminated these structures as possible constitutions for the compounds, m. p. 271° and 219°. It was then found that treatment of (I and II; R = OH) with methyl sulphate and alkali gave, as sole products, the known 6-nitro-3-methyl-4-quinazolone (Bogert and Geiger, *loc. cit.*) and the isomeric 7-nitro-derivative; these compounds, m. p. 197° and 211°, were likewise different from the isomers obtained from the experiments on quaternary salt formation. Independent proof of the orientation of the 6-nitro-compound, m. p. 197°, was obtained through the observation that it was rapidly hydrolysed in hot alkaline solution to 5-nitroanthranilic acid and methylamine; determination of the latter indicated that the reaction was quantitative. In similar fashion, the compound, m. p. 211°, was shown to be 7-*nitro*-3-*methyl*-4-*quinazolone* (as IX); in this case, formic acid was identified in addition to the other products, and the reaction was again quantitative (methylamine determination).

It thus seemed certain that N^1 is the alkylated nitrogen in the compounds, m. p. 271° and 219°, and final proof was obtained by a study of the alkaline degradation of these compounds. The former substance gave a mixture of the known 5-nitro-2-methylaminobenzoic acid (X; R = OH) and its *amide* (X; R = NH_2), and it must therefore be formulated as 6-*nitro*-1-*methyl*-4-*quinazolone* (XI). Hydrolysis of the compound, m. p. 219°, yielded, according to conditions, 4-*nitro*-2-*methylaminobenzoic acid* (XII; R = OH; R′ = H), its *amide* (XII; R = NH_2; R′ = H), and 4-*nitro*-2-N-*methylformamidobenzoic acid* (XII; R = OH; R′ = CHO); the constitution of the first of these products was proved by unambiguous synthesis from methyl 4-nitroanthranilate by tosylation, methylation and two-stage hydrolysis [the *ester* (XII; R = OMe; R′ = H) was a well-defined intermediate], and the structures of the second and third followed from their hydrolysis to the parent acid (XII; R = OH; R′ = H). Representation of the compound, m. p. 219°, as 7-*nitro*-1-*methyl*-4-*quinazolone* (XIII) is obviously the only possible interpretation of these results.

Although purely structural arguments of the above type must be applied with caution to problems involving reactive centres, it is likely that, in 4-hydroxyquinazolines also, the basic centre is N^1 and thus does not coincide with the site of *N*-alkylation. Direct proof, depending on the isolation of quaternary salts of 4-hydroxyquinazolines, is lacking, but 4-hydroxyquinazolines are known to be not readily converted into quaternary salts (Bogert and Geiger, *J. Amer. Chem. Soc.*, 1912, **34**, 683). The importance of differentiating between the centres of basicity and of substitutive alkylation seems to have been largely unrecognised; Tomisek and Christensen (*loc. cit.*), for example, in a discussion of some reactions of 4-substituted quinazolines, have arbitrarily assigned to N^3 the function of proton-acceptance. The American workers may possibly have been influenced by the fact that quinazoline itself quaternises at N^3 (Gabriel and Colman, *Ber.*, 1904, **37**, 3643), but they do not refer to this point, and in any case its evidential value is probably very slight, owing to the decisive influence which may be exerted by 4-substituents in determining the point of maximum basicity (cf. Atkinson and Simpson, *J.*, 1947, 808; Simpson *ibid.*, p. 1653).

In the hydrolysis of the compounds (IX), the initial attack could be regarded as occurring either at N^1–C^2 (hydrolysis of a cyclic amidine) or at N^3–C^4 (hydrolysis of a cyclic amide). In the case of the hydrolysis of (XI) and (XIII), however, amidine-type hydrolysis is more plausible than alternative mechanisms; this initial step involves fission at C^2–N^3 to yield a primary product (as XIV), which by further breakdown could give rise to the various hydrolytic products isolated. Thus the fission of both the 3- and the 1-methylquinazolone may well occur *via* a common initial step, *viz.*, an attack on the amidine double bond, wherever this may be situated in the molecule. In this connexion the recent observations of Leonard and Curtin (*J. Org. Chem.*, 1946, **11**, 341) have some relevance. These workers isolated traces of *o*-aminobenz-*n*-butylamide (XV) during the preparation of 3-*n*-butyl-4-quinazolone (XVI) from 4-hydroxyquinazoline and *n*-butylamine, and consider that both products are derived from a common intermediate (XVII). We now suggest, as a more likely explanation, that (XV) arises by hydrolysis of (XVI) as a result of the amidine characteristics of the latter; further hydrolysis of (XV) to anthranilic acid, which would complete the analogy with the quinazolones (IX), was not observed, but might well be unlikely to occur under the conditions used (excess of butylamine in a sealed tube).

The facile alkaline and acid hydrolysis of 4-amino- to 4-hydroxy-quinazolines are readily explained by the amidine mechanism, on the assumption that such compounds react, in these hydrolyses, in the imino-dihydro- (semicyclic amidine) and not in the amine (cyclic amidine) form. By way of contrast, 4-hydroxyquinazoline and (I and II; R = OH) are not appreciably attacked under more drastic alkaline conditions. The difference in reactivity between the hydroxyquinazolines and the quinazolones may be regarded as the result of the fixation, by *N*-alkylation, of a non-aromatic system in the latter compounds; the amidine characteristics are thus enhanced, but are suppressed if the potential cyclic amidine group is included in, and thus subordinated to, the more stable " aromatic " system of the hydroxy-compounds. The behaviour of the 4-aminoquinazolines is consistent with the idea that the " amino-aromatic " forms are, similarly, resistant to hydrolysis under the conditions used, but that, owing to their existence in equilibrium with the non-aromatic imino-dihydro-tautomers and to the susceptibility of the latter to hydrolysis, a progressive conversion into the hydroxy-compounds occurs. According to this mechanism, the reactivity of the aminoquinazolines is to be distinguished from the superficially similar hydrolysis of the 4-acetamido- and 4-phenoxyquinazolinium compounds; here, the reactivity of the 4-substituent is engendered by electromeric shift induced by N^1 (as in heterocyclic quaternary compounds with reactive methyl groups) with accompanying entry of hydroxyl ion. In this connexion, the conversion of 2-chloro-5-phenoxyacridine (XVIII) into 2-chloro-10-methylacridone (XIX) in 85% yield by reaction with methyl *p*-toluenesulphonate (Drozdov and Skljarov, *J. Gen. Chem. Russia*, 1944, **19**, 945) is highly relevant; the reaction is strikingly similar to that shown by 6- and 7-nitro-4-phenoxyquinazoline, and strengthens the view that the behaviour of these compounds on conversion into quaternary salts is not to be attributed to the potential amidine characteristics of the quinazoline nucleus.

Experimental.

(Melting points are uncorrected.)

6-Nitro-4-hydroxyquinazoline.—The following conditions were superior to those given by Bogert and Geiger (*loc. cit.*). 4-Hydroxyquinazoline (20 g.) was added during 30—40 minutes to a mixture of nitric acid (*d* 1·53, 40 c.c.) and concentrated sulphuric acid (40 c.c.), care being taken that the temperature did not exceed 95°; the solution was then heated on the steam-bath for ½ hour and poured into water (1·5 l.); pure 6-nitro-4-hydroxyquinazoline separated, m. p. 275—277° (22·2 g., 85%).

Bogert and Scatchard (*loc. cit.*) give m. p. 286—287° (corr.); Bogert and Geiger (*loc. cit.*) give m. p. 284° (uncorr.); Magidson and Golovchinskaya (*loc. cit.*) give m. p. 275°. This compound was recovered in quantitative, and the 7-nitro-isomer (*q.v.*) in almost quantitative, yield after being refluxed for ½ hour with 2N-sodium hydroxide.

7-*Nitro*-4-*hydroxyquinazoline*.—4-Nitroanthranilic acid (50 g.) and formamide (50 g.) were gently refluxed for 40 minutes; addition of water (100 c.c.) to the cooled mass and filtration, followed by washing with alcohol, gave the pure nitro-compound, m. p. 268—270° (50·5 g., 96%). Bogert and Klaber (*loc. cit.*) give m. p. 276° (corr.).

4-*Chloro*-6-*nitroquinazoline*.—An intimate mixture of the hydroxy-compound (20 g.) and phosphorus pentachloride (32·8 g.) was heated at 160° (bath temp.) for 2½ hours, during which time a clear solution was formed. Ligroin (b. p. 60—80°, 750 c.c.) was added to the cold mixture, and the crude chloro-compound (19 g.) filtered off and washed with more ligroin. The pure compound could be obtained by suspension of the crude material in dilute sodium hydroxide and extraction with chloroform, from which it separated in pale, yellow-green prismatic needles, m. p. 130—131° (U.S.P. 1,880,447 gives m. p. 128°; Magidson and Golovchinskaya, *loc. cit.*, give m. p. 129°).

4-*Chloro*-7-*nitroquinazoline*.—7-Nitro-4-hydroxyquinazoline (20 g.), phosphorus pentachloride (30 g.), and phosphorus oxychloride (60 c.c.) were gently refluxed for 2 hours. Addition of ligroin (b. p. 60—80°, 750 c.c.) to the cold mixture gave the crude chloro-compound (20 g.), which, when purified in the same manner as the 6-nitro-isomer, formed almost colourless prismatic needles, m. p. 148—149° (U.S.P. 1,880,447 gives m. p. 148°).

6-*Nitro*-4-*phenoxyquinazoline*.—The crude chloro-compound from 6-nitro-4-hydroxyquinazoline (10 g.) was heated for 1 hour with a solution of potassium hydroxide (6 g.) in phenol (60 g.) at 90—95°. The melt was poured into dilute sodium hydroxide and extracted with ether, the extract washed with aqueous sodium hydroxide and water, dried, and concentrated, giving 6-*nitro*-4-*phenoxyquinazoline* (6·1 g.), which crystallised from alcohol in colourless needles, m. p. 148—149° (Found: C, 62·7; H, 3·6; N, 15·5. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%).

7-*Nitro*-4-*phenoxyquinazoline*.—Prepared similarly to the above isomer [using crude chloroquinazoline from 7-nitro-4-hydroxyquinazoline (15 g.), potassium hydroxide (7 g.), and phenol (70 g.)], this *compound* (14·7 g.) formed colourless needles, m. p. 173·5—174°, from alcohol (Found: C, 62·7; H, 3·55; N, 15·4. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4; N, 15·7%).

6-*Nitro*-4-*aminoquinazoline*.—(*a*) Crude 4-chloro-6-nitroquinazoline (from 20 g. of hydroxy-compound) was added to a mixture of phenol (80 g.) and powdered ammonium carbonate (40 g.). After 1 hour at 90—95°, the mixture was diluted with water, excess of aqueous sodium hydroxide added, and the solid collected (20·2 g., m. p. 270—300°). This was added to ammonium acetate (100 g.) which had just been fused, and kept at 180° (bath temp.) for ½ hour. The cold melt was diluted with water, filtered, and the crude amine dissolved in warm hydrochloric acid (0·4N, 250 c.c.). The filtered solution was basified with ammonia, yielding crude 6-*nitro*-4-*aminoquinazoline*, m. p. 316—319° (15·4 g.; 77% based on hydroxy-compound). The pure amine formed hair-like lemon-yellow needles, m. p. 320—320·5°, from hot water (Found: C, 51·1; H, 2·7; N, 29·2. $C_8H_6O_2N_4$ requires C, 50·5; H, 3·2; N, 29·5%). The amine was converted almost quantitatively into 6-nitro-4-hydroxyquinazoline (m. p. and mixed m. p.) after it had been heated under reflux with N-sodium hydroxide solution for ½ hour, and a similar result was obtained with the 7-nitro-isomer (*q.v.*). Both amines, and also the corresponding acetamido-compounds (*q.v.*), were hydrolysed to the hydroxyquinazolines when boiled with 2N-hydrochloric acid for ½—1 hour.

(*b*) Pure chloro-compound (1 g.), left at room temperature under ammonia solution (*d* 0·88, 20 c.c.) for 4 days in a closed vessel, yielded unchanged material (70 mg.), and the 4-amino-compound (0·76 g., m. p. and mixed m. p. 317—319°).

7-*Nitro*-4-*aminoquinazoline*.—(*a*) Treatment as in (*a*) above of crude 4-chloro-7-nitroquinazoline (from 20 g. of the hydroxyquinazoline) gave a mixture, m. p. 265—270° (15·5 g.); fusion of this with ammonium acetate (77 g.) and purification as already described gave 7-*nitro*-4-*aminoquinazoline* (69% yield based on hydroxy-compound), which crystallised from water in long, pale yellow needles, m. p. 303—305° (Found: C, 50·9; H, 3·4; N, 29·7. $C_8H_6O_2N_4$ requires C, 50·5; H, 3·2; N, 29·5%).

(*b*) Extraction of the foregoing mixture, m. p. 265—270° (5·6 g.), with boiling alcohol gave 7-nitro-4-phenoxyquinazoline (1·7 g., m. p. 168—170°, identified by mixed m. p.); the alcohol-insoluble residue yielded 7-nitro-4-aminoquinazoline (1 g.), m. p. 299—300°, not depressed by admixture with authentic material

(*c*) Pure 4-chloro-7-nitroquinazoline (1 g.), treated exactly as the 6-nitro-isomer with ammonia solution as described in (*b*) above, yielded unchanged material (0·49 g.) and 7-nitro-4-aminoquinazoline (0·37 g.).

6-*Nitro*-4-*acetamidoquinazoline*.—The amine (10 g.) and acetic anhydride (100 c.c.) were refluxed for ½ hour; the *acetamido*-compound, formed in almost quantitative yield, was isolated by filtration and washing with ether. It crystallised from acetic acid in small, pale yellow needles, m. p. 262—263° (decomp.) (Found: C, 51·5; H, 3·8; N, 24·15. $C_{10}H_8O_3N_4$ requires C, 51·7; H, 3·5; N, 24·1%).

7-*Nitro*-4-*acetamidoquinazoline*.—Prepared similarly to the above compound and in similar yield, this *compound* separated from acetic acid in small, pale yellow needles, m. p. 240—242° (decomp.) (Found: C, 51·75; H, 3·75; N, 24·5. $C_{10}H_8O_3N_4$ requires C, 51·7; H, 3·5; N, 24·1%).

6-*Nitro*-4-*methoxyquinazoline*.—A solution of pure 4-chloro-6-nitroquinazoline (2 g.) and sodium methoxide (0·6 g.) in methyl alcohol (50 c.c.) was refluxed for ½ hour and diluted with water, yielding 6-*nitro*-4-*methoxyquinazoline* (1·54 g., 75%) as glistening yellow prismatic needles, m. p. 118—119° after recrystallisation from 50% aqueous methanol (Found: C, 52·7; H, 3·5; N, 19·9. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4; N, 20·5%).

7-*Nitro*-4-*methoxyquinazoline*.—Prepared similarly to the above isomer, 7-*nitro*-4-*methoxyquinazoline* (yield, 90%) separated from aqueous methanol in small, soft, colourless needles, m. p. 137—138° (Found: C, 52·85; H, 3·4. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4%).

6-*Nitro*-4-*anilinoquinazoline*.—Crude 4-chloro-6-nitroquinazoline (from 10 g. of hydroxy-compound),

50% aqueous acetone (100 c.c.), aniline (5 c.c.), and concentrated hydrochloric acid (0·5 c.c.) were refluxed for ½ hour. The mixture was then basified with aqueous ammonia, and the solid (m. p. 235—237°; 12·2 g.; 87% based on hydroxy-compound) crystallised from aqueous acetic acid, giving 6-*nitro*-4-*anilinoquinazoline* as yellow needles, m. p. 236—237·5° (decomp.) (Found: C, 63·0; H, 4·0; N, 21·5. $C_{14}H_{10}O_2N_4$ requires C, 63·15; H, 3·8; N, 21·0%).

6-*Amino*-4-*anilino*-1-*methylquinazolinium Iodide*.—6-Nitro-4-anilinoquinazoline (10 g.) and methyl *p*-toluenesulphonate (7·7 g.) were mixed and heated at 148—150° for 30 minutes; as the temperature was raised to this point, the original melt became pasty, and solidified at *ca.* 140°. The cold mass was digested with hot alcohol (100 c.c.), cooled, and the solid (14·6 g.; 85%; m. p. 247—248°) collected and crystallised from hot water, yielding soft, deep yellow needles, m. p. 249—250° (decomp.), of 6-*nitro*-4-*anilino*-1-*methylquinazolinium* p-*toluenesulphonate* (Found: C, 58·25; H, 4·6; N, 12·8; S, 7·1. $C_{22}H_{20}O_5N_4S$ requires C, 58·4; H, 4·45; N, 12·4; S, 7·1%). Addition of potassium iodide (29·2 g.) to a solution of the salt (14·6 g.) in hot water (550 c.c.) precipitated the *iodide* (11·6 g.; 88%); this crystallised from water in massive, yellow, prismatic needles, m. p. 247—248° (decomp.) (Found: C, 43·9; H, 3·65; N, 13·8. $C_{15}H_{13}O_2N_4I$ requires C, 44·1; H, 3·2; N, 13·7%). Occasionally a second crystalline form, m. p. 254—256° (decomp.), was obtained. A solution of the iodide (1 g.) in hot water (60 c.c.) was treated at 91—93° with iron powder (1·25 g.), added in portions during ½ hour with mechanical stirring; after a further ½ hour's stirring and heating, pure 6-*amino*-4-*anilino*-1-*methylquinazolinium iodide* (0·67 g.) separated from the filtered solution in glittering golden needles, m. p. 287—288° (Found: C, 47·7; H, 4·1; N, 15·4. $C_{15}H_{15}N_4I$ requires C, 47·6; H, 4·0; N, 14·8%). Concentration of the filtrate gave a further 0·16 g. (total yield, 89%).

7-*Nitro*-4-*anilinoquinazoline*.—Prepared similarly to the 6-nitro-isomer, this *compound* [9·7 g. (70%) from 10 g. of hydroxy-compound] crystallised from glacial acetic acid in stout yellow needles, m. p. 251—252° (decomp.) (Found: C, 62·7; H, 3·55; N, 21·1. $C_{14}H_{10}O_2N_4$ requires C, 63·15; H, 3·8; N, 21·0%).

7-*Amino*-4-*anilino*-1-*methylquinazolinium Iodide*.—This salt and its precursors were prepared as for the above 6-substituted derivatives; each salt was crystallised from water. 7-*Nitro*-4-*anilino*-1-*methylquinazolinium* p-*toluenesulphonate*, soft yellow needles, had m. p. 257—258° (decomp.) (yield, 92%) (Found: C, 58·6; H, 4·8; N, 12·5; S, 7·1. $C_{22}H_{20}O_5N_4S$ requires C, 58·4; H, 4·45; N, 12·4; S, 7·1%). The *iodide*, m. p. 256—257° (decomp.) (yield, 93%), formed lustrous, orange-red, prismatic needles (Found: C, 44·1; H, 3·8; N, 14·2. $C_{15}H_{13}O_2N_4I$ requires C, 44·1; H, 3·2; N, 13·7%). 7-*Amino*-4-*anilino*-1-*methylquinazolinium iodide* (yield, 90%) crystallised in brownish-yellow rectangular rods, m. p. 266—268° after melting at 210° and then resolidifying (Found: C, 45·5; H, 4·65; N, 14·9. $C_{15}H_{15}N_4I,H_2O$ requires C, 45·5; H, 4·3; N, 14·2%).

Preparation and Decomposition of 6-*Nitro*-3-*methyl*-4-*quinazolone*.—A solution of 6-nitro-4-hydroxyquinazoline (1 part) in the minimum volume (24 parts) of 2% aqueous potassium hydroxide was stirred at 50° with methyl sulphate (0·5 part by volume); the *N*-methyl ether (yield, 75%) separated from alcohol in minute yellow needles, m. p. 196—197° [Bogert and Geiger, *loc. cit.*, give m. p. 196° (corr.)]. The use of excess of alkali gave a somewhat lower yield. Decompositions of this compound were carried out as follows:

(*a*) The compound (0·5 g.) was refluxed with aqueous sodium hydroxide (2N, 10 c.c.) for ½ hour, the evolved gas being passed into water and identified as methylamine by conversion into the picrate, m. p. and mixed m. p. 205—207°. Acidification of the alkaline solution gave 5-nitroanthranilic acid (0·36 g.), m. p. and mixed m. p. 276—277° (from acetic acid) (acetyl derivative, m. p. and mixed m. p. 221—222°).

(*b*) In quantitative experiments, using excess of 2N-sodium hydroxide, 95·2 and 95·6% of the theoretical amount of methylamine was evolved; blank tests with known amounts of methylamine gave (mean of two) 94·7%.

Preparation and Decomposition of 7-*Nitro*-3-*methyl*-4-*quinazolone*.—Prepared similarly to the foregoing isomer, this *compound* (yield, 85%) formed small, cream-coloured needles, m. p. 210—211°, from alcohol (Found: C, 52·9; H, 3·6; N, 20·3. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4; N, 20·5%). The alkaline decomposition was carried out as above. Methylamine was identified as picrate. Acidification of the alkaline solution with phosphoric acid gave 4-nitroanthranilic acid (0·31 g.), m. p. 256—258° alone and when mixed with authentic material; the filtrate from this acid was distilled, and formic acid identified in the distillate by neutralisation, concentration, and conversion into *p*-bromoformanilide, m. p. and mixed m. p. 115—116°, in faintly acid solution. Quantitative experiments carried out under the conditions used for the 6-nitro-isomer gave 95·2 and 95·0% of the theoretical amount of methylamine (blank, 94·7%).

6-*Nitro*-1-*methyl*-4-*quinazolone*.—(*a*) An intimate mixture of 6-nitro-4-acetamidoquinazoline (5 g.) and methyl *p*-toluenesulphonate (4·2 g.) was heated in an oil-bath; reaction occurred at 160° (bath temp.), and after 10 minutes the viscous melt was cooled and extracted with hot water (100 c.c.). Concentrated hydrochloric acid (50 c.c.) was added to the aqueous solution, from which, after ½ hour's refluxing, solvent was removed in an evacuated desiccator. Digestion of the residue with alcohol (30 c.c.) gave a crystalline mass [4·6 g., m. p. 213—216° (decomp.)]; this was dissolved in water (20 c.c.), and the filtered (charcoal) solution was treated with ammonia solution (4N, 5 c.c.), yielding crude 6-*nitro*-1-*methyl*-4-*quinazolone* (1·9 g., m. p. 257—259°), which on recrystallisation from water (charcoal) formed long colourless needles, m. p. 272—273° (Found: C, 53·0; H, 3·7; N, 20·6. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4; N, 20·5%).

(*b*) 6-Nitro-4-phenoxyquinazoline (1 g.) and methyl *p*-toluenesulphonate (0·7 g.) were heated to 125° (bath temp.). The clear orange melt then began to crystallise, and the reaction was complete after 15 minutes at 150°. The product was crystallised from alcohol–acetone, and finally from alcohol alone, yielding 6-*nitro*-1-*methyl*-4-*quinazolone* p-*toluenesulphonate* (1 g.) in colourless fluffy needles, m. p. 234—235° [237—238° when mixed with an authentic sample, m. p. 237—238°, prepared from an alcoholic solution of *p*-toluenesulphonic acid and the base prepared by method (*a*)] (Found: C, 48·6; H, 4·4; N, 10·9; S, 7·9. $C_{16}H_{15}O_6N_3S,H_2O$ requires C, 48·6; H, 4·3; N, 10·6; S, 8·1%). The salt dissolved

in hot water to form a strongly acid solution, from which 6-nitro-1-methyl-4-quinazolone, m. p. 271—272° (alone and mixed with the sample described above), separated on cooling (Found: C, 53·2; H, 3·4; N, 20·3%).

Alkaline Decomposition of 6-*Nitro*-1-*methyl*-4-*quinazolone*.—(*a*) A solution of the quinazolone (0·2 g.) in hot water (21 c.c.) was treated with 2N-sodium hydroxide (5 c.c.); an immediate and copious crystallisation of 5-*nitro*-2-*methylaminobenzamide* (0·2 g.) occurred; this substance formed brittle yellow needles, m. p. 218—218·5°, from water containing a little acetic acid (Found: C, 49·3; H, 4·8; N, 21·8. $C_8H_9O_3N_3$ requires C, 49·25; H, 4·65; N, 21·5%). The amide was unchanged after short boiling with 2N-hydrochloric acid, but was hydrolysed completely to the acid under the same conditions as those used in the following experiment.

(*b*) The quinazolone (1 g.), 2N-sodium hydroxide solution (20 c.c.), and water (30 c.c.) were refluxed for 40 minutes; ammonia was evolved, and a clear solution was gradually formed. Acidification precipitated 5-nitro-2-methylaminobenzoic acid, which formed brittle yellow needles, m. p. 263—264° (decomp.), from acetic acid. Thieme (*J. pr. Chem.*, 1891, **43**, 471) gives m. p. 259°; Blanksma (*Rec. Trav. chim.*, 1902, **21**, 269), m. p. 259°; and Keller (*Arch. Pharm.*, 1908, **246**, 1), m. p. 258°. The acid gave a negligible depression in m. p. on admixture with 5-nitroanthranilic acid, but was distinguished from the latter by its negative diazo-reaction and by its conversion into *methyl* 5-*nitro*-2-*methylaminobenzoate*; this ester, obtained by means of methanolic sulphuric acid, crystallised from methanol in long, pale greenish-yellow needles, m. p. 146—147° (124—126° when mixed with methyl 5-nitroanthranilate, m. p. 167—168°) (Found: C, 51·2; H, 4·9; N, 13·3. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·8; N, 13·3%).

7-*Nitro*-1-*methyl*-4-*quinazolone*.—(*a*) 7-Nitro-4-acetamidoquinazoline (5 g.) was treated exactly as already described for the 6-nitro-isomer. The product obtained by refluxing with hydrochloric acid, removal of solvent, and digestion with alcohol, crystallised from water in red-tinged plates, m. p. 252—254° (3·1 g.). Basification of a hot aqueous solution with ammonia furnished 7-*nitro*-1-*methyl*-4-*quinazolone* (1·27 g.), which formed massive, prismatic, flesh-coloured needles, m. p. 215—216° (Found: C, 49·7; H, 4·1; N, 19·4. $C_9H_7O_3N_3,\frac{2}{3}H_2O$ requires C, 49·8; H, 3·8; N, 19·35%).

(*b*) Fusion of 7-nitro-4-phenoxyquinazoline (5·2 g.) and methyl *p*-toluenesulphonate (3·8 g.) at 150° for ¾ hour gave almost colourless needles (5·8 g.) of 7-*nitro*-1-*methyl*-4-*quinazolone* p-*toluenesulphonate*, m. p. 247—247·5°, sparingly soluble in hot alcohol, readily in boiling water (from which it could be recrystallised without decomposition), and yielding the quinazolone (m. p. 218—219°, identified by mixed m. p.) on basification (Found: C, 48·4; H, 4·05; N, 10·3; S, 7·7. $C_{16}H_{15}O_6N_3S,H_2O$ requires C, 48·6; H, 4·3; N, 10·6; S, 8·1%). A sample of the salt prepared from the base [from method (*a*)] and *p*-toluenesulphonic acid in alcoholic solution had m. p. and mixed m. p. 251—252°.

Alkaline Decomposition of 7-*Nitro*-1-*methyl*-4-*quinazolone*.—(*a*) Addition of aqueous sodium hydroxide (2N, 5 c.c.) to a solution of the quinazolone (1 g.) in hot water (35 c.c.) produced an immediate red coloration, followed by rapid separation of 4-*nitro*-2-*methylaminobenzamide* (0·27 g.); this substance crystallised from methanol in bundles of massive, orange prismatic needles, m. p. 188—189° (Found: C, 49·2; H, 4·6; N, 21·9. $C_8H_9O_3N_3$ requires C, 49·25; H, 4·65; N, 21·5%). The filtrate from this amide was acidified with phosphoric acid (to Congo-red), and the resultant 4-*nitro*-2-N-*methylformamidobenzoic acid* (0·56 g.) recrystallised from aqueous methanol, yielding light, yellow needles, m. p. 203—204° (efferv.) (Found: C, 47·8; H, 3·9; N, 13·0. $C_9H_8O_5N_2$ requires C, 48·2; H, 3·6; N, 12·5%). Distillation of the filtrate from this acid gave formic acid, identified as *p*-bromoformanilide in the manner already described.

(*b*) When a solution of the quinazolone (0·2 g.) in hot water (7 c.c.) and aqueous sodium hydroxide (2N, 5 c.c.) was refluxed for 10 minutes, ammonia was evolved, and 4-*nitro*-2-*methylaminobenzoic acid* (0·17 g.) was precipitated on acidification; recrystallisation of this from acetic acid or aqueous methanol gave glittering, orange-red, prismatic needles, m. p. 259—260° (decomp.) alone and when mixed with the synthetic acid described below (unlike the 5-nitro-isomer, a marked depression in m. p. was observed in admixture with the corresponding nitroanthranilic acid) (Found: C, 49·2; H, 4·2. $C_8H_8O_4N_2$ requires C, 49·0; H, 4·1%). The acid was also obtained by refluxing either the amide or the formamido-acid described above with excess of N-sodium hydroxide for ½ hour.

Synthesis of 4-*Nitro*-2-*methylaminobenzoic Acid*.—A solution of methyl 4-nitroanthranilate (5 g.) in pyridine (50 c.c.) was treated in the cold with *p*-toluenesulphonyl chloride (7 g.) and left for 2 days. The solid which had separated (5·8 g.) was collected and recrystallised from aqueous pyridine; *methyl* 4-*nitro*-2-p-*toluenesulphonamidobenzoate* separated in long, colourless blades, m. p. 183—184° (Found: C, 51·5; H, 4·35. $C_{15}H_{14}O_6N_2S$ requires C, 51·4; H, 4·0%). A suspension of the tosyl derivative (3 g.) in alcohol (30 c.c.) was treated dropwise, with shaking, with the calculated quantity of aqueous sodium hydroxide (*ca.* 0·3N); partial solution occurred, followed by rapid separation of a yellow sodium salt. A suspension of the dry salt (3 g.) in acetone (60 c.c.) was gently refluxed with methyl iodide (12 c.c.) for 4 hours; filtration and concentration yielded *methyl* 4-*nitro*-2-p-*toluenesulphonmethylamidobenzoate* (2·75 g.), which separated from methanol in small, colourless rods, m. p. 126—128° (Found: C, 52·6; H, 4·7. $C_{16}H_{16}O_6N_2S$ requires C, 52·7; H, 4·4%). A solution of this (2 g.) in concentrated sulphuric acid (10 c.c.) was kept at 80—90° for ½ hour and then poured into water, yielding *methyl* 4-*nitro*-2-*methylaminobenzoate* (1·2 g.). This ester crystallised from slightly aqueous methanol in long, soft, orange needles, m. p. 124—125° (Found: C, 51·5; H, 4·6; N, 13·3. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·8; N, 13·3%); it was only partly hydrolysed by 5N-hydrochloric acid (1 hour's reflux), but was smoothly converted by N-sodium hydroxide (½ hour's reflux) into 4-nitro-2-methylaminobenzoic acid, m. p. 259—260° (decomp.) after recrystallisation from acetic acid.

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WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

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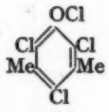
89. *Halogenation of* m-5- *and* m-2-*Xylenols. Preparation and Structure of Certain Polyhalogeno-*m-5- *and* -m-2-*xylenols.*

By C. H. R. Elston, A. T. Peters, and (the late) F. M. Rowe.

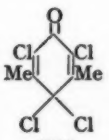
Chemical and absorption-spectra data are examined in an attempt to clarify the constitution of certain polyhalogeno-phenols and -xylenols, and the respective merits of the quinonoid and hypohalite configurations are discussed. 1 Mol. of chlorine and 1 mol. of 2 : 4 : 6-tribromo-*m*-5-xylenol afford 2-*chloro*-2 : 4 : 6-*tribromo*-1 : 3-*dimethyl*cyclo*hexa*-3 : 6-*diene*-5-*one* (VI), but 2·5 mols. of chlorine cause replacement of bromine to give the 2 : 2 : 4-*trichloro*-6-*bromo*-analogue of (VI). 2 : 4 : 6-*Trichloro*-m-5-*xylenol bromide* (VIII) and 4 : 5 : 6-*tribromo*-m-2-*xylenol chloride* and *bromide* are characterised. Chlorination of 4 : 6-dichloro-2-bromo-*m*-2-xylenol yields, with replacement of bromine, 2 : 2 : 4 : 6-tetrachloro-1 : 3-dimethyl*cyclo*hexa-3 : 6-diene-5-one.

In view of the work of Lauer (*J. Amer. Chem. Soc.*, 1926, **48**, 442) and of Ssuknewitsch and Budnitzky (*J. pr. Chem.*, 1933, **138**, 22), it is possible that 2 : 2 : 4 : 6-tetrachloro-1 : 3-dimethyl-*cyclo*hexa-3 : 6-diene-5-one may possess a hypohalite (I) rather than a hemiquinonoid structure (II).

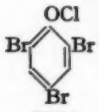
The above workers showed that different isomerides, $C_6H_2OClBr_3$, were obtained from the action of chlorine water on 2 : 4 : 6-tribromophenol, and of bromine water on 4-chloro-2 : 6-dibromophenol, whereas the quinonoid configuration would require them to be identical (V). The same workers favour the respective hypohalite structures (III) and (IV), but Lauer (*loc. cit.*) postulates a partial rearrangement of phenol chlorides with a *p*-bromine atom into *p*-chlorophenol bromides. We found that chlorination of 2 : 4 : 6-tribromophenol gives 2 : 4 : 6-tribromophenol chloride, which is readily decomposed by passing sulphur dioxide through its alcohol solution, to give a mixture of trihalogenophenols, *i.e.*, there is loss of bromine *and* chlorine. On the other hand, 4-chloro-2 : 6-dibromophenol and bromine give 4-chloro-2 : 6-dibromophenol bromide, which decomposes with loss of bromine only, to yield 4-chloro-2 : 6-dibromophenol.



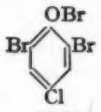
(I.)



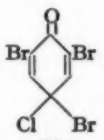
(II.)



(III.)



(IV.)



(V.)

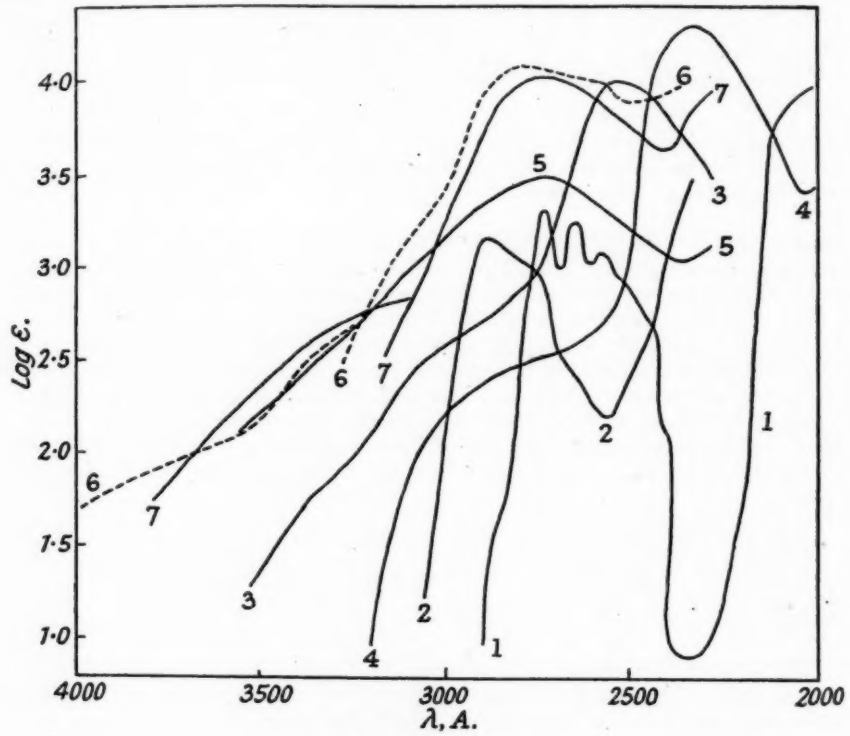
We suggest that a possible explanation of the above results is that chlorine reacts with 2 : 4 : 6-tribromophenol to give (III), which then tautomerises to some extent to (V), and thence to some (IV); bromine and 4-chloro-2 : 6-dibromophenol, however, give (IV), which tautomerises to (V) to a very small extent only. (III) would probably lose chlorine on degradation, whereas (IV) and (V) would probably lose bromine.

A mixed m. p. curve of 2 : 4 : 6-tribromophenol and 4-chloro-2 : 6-dibromophenol, or of their respective methyl ethers, showed little depression in m. p. of mixtures, and this method of identification is unreliable, a factor noted in other cases of related trihalogeno-*m*-xylenols. It was considered that a study of absorption spectra might clarify the position. Accordingly, freshly-prepared specimens of 2 : 4 : 6-tribromophenol chloride, 2 : 2 : 4 : 6-tetrachloro-1 : 3-dimethyl*cyclo*hexa-3 : 6-diene-5-one, and 2 : 4 : 6-trichloro-*m*-5-xylenol were sent to Dr. C. B. Allsopp and Miss D. M. Simpson, of Cambridge University, to whom our warm appreciation and thanks are due. These workers plotted absorption curves in *cyclo*hexane and compared them with those obtained from phenol and benzoquinone, respectively.

There is close similarity between the curves for 2 : 4 : 6-trichloro-*m*-5-xylenol and phenol, as expected, and the effect of the chlorine is to displace the band to slightly longer wave-lengths and to reduce the intensity. The curve for the tetrachloro-compound is similar to that for benzoquinone. 2 : 4 : 6-Tribromophenol chloride gave a similar curve to that for the quinone, although there seemed to be a breakdown in Beer's law at a certain concentration, and it is possible that some change in structure occurs. The results can be given only in support, but not proof, of the quinonoid structure for the polyhalogeno-compounds, as no comparison was possible with a curve obtained from a compound of definite hypohalite structure. We do, however, consider that the properties of the tetrachloro-compound are best explained on the quinonoid basis (II).

Work was then begun to compare the identity or otherwise of the products of:

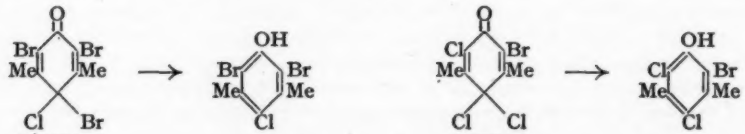
(i) chlorination of 2 : 4 : 6-tribromo-*m*-5-xylenol and bromination of 2-chloro-4 : 6-dibromo-*m*-5-xylenol, and (ii) bromination of 2 : 4 : 6-trichloro-*m*-5-xylenol, and chlorination of 4 : 6-dichloro-2-bromo-*m*-5-xylenol. Chlorine (1 mol.) and 2 : 4 : 6-tribromo-*m*-5-xylenol in acetic acid at below 30° gave, probably, 2-*chloro*-2 : 4 : 6-*tribromo*-1 : 3-*dimethyl*cyclo*hexa*-3 : 6-*diene*-5-*one* (VI), decomposed by boiling alcohol, or sulphur dioxide in aqueous alcohol, to give a trihalogeno-compound which appeared to be 2-chloro-4 : 6-dibromo-*m*-5-xylenol. The mixed m. p. method being unreliable, it is important that full analyses and general properties be examined.



Absorption curves.

1. *Phenol.*
2. 2:4:6-*Trichloro*-m-5-*xylenol.*
3. *Tetrachloro*-m-5-*xylenol.*
4. *Benzoquinone.*
5. *Tetrabromo*-m-2-*xylenol.*
6, 7. 2:4:6-*Tribromophenol chloride* (*two specimens*).

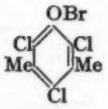
The action of chlorine (2·5 mols.) on 2 : 4 : 6-tribromo-*m*-5-xylenol at 10°, gave a trichlorobromo-derivative, probably 2 : 2 : 4-*trichloro*-6-*bromo*-1 : 3-*dimethyl*cyclo*hexa*-3 : 6-*diene*-5-*one* (VII), which on removal of labile halogen yielded a compound whose analysis and properties agreed with those of 2 : 6-dichloro-4-bromo-*m*-5-xylenol.



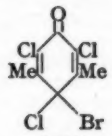
(VI.) (VII.)

Bromine did not react with 2-chloro-4 : 6-dibromo-*m*-5-xylenol to give a polyhalogeno-derivative, although a variety of conditions was examined: it did, however, react with 2 : 4 : 6-trichloro-*m*-5-xylenol in acetic acid to give a very unstable trichlorobromo-compound, probably 2 : 4 : 6-*trichloro*-*m*-5-*xylenol bromide* (VIII), with some tautomeric form (IX); the product lost bromine readily on boiling with alcohol, to give 2 : 4 : 6-trichloro-*m*-5-xylenol. Chlorination of 4 : 6-dichloro-2-bromo-*m*-5-xylenol provided interesting results. The main product was 2 : 2 : 4 : 6-tetrachloro-1 : 3-dimethyl*cyclo*hex-3 : 6-diene-5-one, identical with that

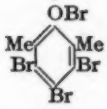
prepared by chlorination of *m*-5-xylenol. It was separated by careful fractional crystallisation of the reaction product from light petroleum, followed by separation of the crystals by mechanical means. This affords a further instance of the ease of elimination of bromine by chlorine in this series. A second product was not identified.



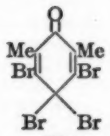
(VIII.)



(IX.)



(X.)



(XI.)

Addition of 4 : 5 : 6-tribromo-*m*-2-xylenol to aqueous bromine gave a tetrabromo-compound, probably mainly 4 : 5 : 6-*tribromo*-m-2-*xylenol bromide* (X), with a little of the quinonoid form (XI). Removal of labile bromine with sulphur dioxide in alcohol gave 4 : 5 : 6-tribromo-*m*-2-xylenol, whereas zinc dust and water afford the same tribromo-compound with some 4 : 5-dibromo-*m*-2-xylenol.

The absorption curve of compound (X) conforms to the quinonoid type, although there was possibly some change in *cyclo*hexane solution.

Tetrabromo-*m*-2-xylenol and aqueous potassium iodide gave a red *adduct* of 2 mols. of 4 : 5 : 6-tribromo-*m*-2-xylenol and 1 mol. of 4 : 6-dibromo-*m*-xyloquinone, the constitution of which was confirmed by synthesis.

Chlorine and 4 : 5 : 6-tribromo-*m*-2-xylenol in acetic acid yielded 4 : 5 : 6-*tribromo*-m-2-*xylenol chloride*, which loses its chlorine in boiling alcohol, or with zinc dust and water affords a mixture of 4 : 5-dibromo- and 4 : 5 : 6-tribromo-*m*-2-xylenol. The only products isolated from the interaction of bromine and 5-chloro-4 : 6-dibromo-*m*-2-xylenol were 4 : 6-dibromo-*m*-xyloquinone and an adduct, m. p. 138—140°, identical with that synthesised from 1 mol. of the above quinone and 2 mols. of 5-chloro-4 : 6-dibromo-*m*-2-xylenol.

Experimental.

2 : 4 : 6-*Tribromophenol Chloride*.—Saturated chlorine water (2000 c.c.; chlorine, 16 g., 4·4 mols.) was added to a paste of 2 : 4 : 6-tribromophenol (16 g.; 1 mol.) in water (20 c.c.) at room temperature. The yellow precipitate was filtered off, dissolved in ether, the solution dried, and solvent removed under reduced pressure until yellow needles began to separate. The *product* crystallised from ether in fine, yellow needles, m. p. 125—130° (decomp.) (Found: 0·1188 g. gave 0·2233 g. of AgCl + AgBr. Calc. for $C_6H_2OClBr_3$: AgCl + AgBr, 0·2328 g.). A trace of chloranil was recovered from the ether mother-liquors. On passing sulphur dioxide through an alcoholic solution of the yellow needles until decolorised, and diluting with water, almost colourless needles separated, m. p. 79—82°, with previous softening (Found in crude product: C, 23·3, 24·7; H, 1·3, 1·4; 2 mg. gave 3·48 mg. of AgCl + AgBr. Calc. for $C_6H_3OBr_3$: C, 21·7; H, 1·0%; AgCl + AgBr, 3·408 mg. $C_6H_2OClBr_2$ requires C, 25·1; H, 1·05%; AgCl + AgBr, 3·63 mg.), probably a mixture of 2 : 4 : 6-tribromo- and 4-chloro-2 : 6-dibromophenol. Crystallisation from light petroleum yielded colourless needles, m. p. 86—87° (Found: C, 22·9, 22·85; H, 1·0, 1·3%; 2 mg. gave 3·48 mg. AgCl + AgBr) of a mixed trihalogeno-compound.

4-*Chloro*-2 : 6-*dibromophenol Bromide*.—Bromine (8·8 g.; 1·1 mols.) in acetic acid (30 c.c.) and water (460 c.c.) was added to a suspension of 4-chloro-2 : 6-dibromophenol (14·3 g.; 1 mol.) in the minimum amount of water. After 3 hours' stirring at room temperature, the product was filtered off; it crystalllsed from ether in pale yellow needles, m. p. 99—100°, decomp. at 120° (Found: 0·0989 g. gave 0·1910 of AgCl + AgBr. Calc. for $C_6H_2OClBr_3$: AgCl + AgBr, 0·1916 g.).

Degradation with sulphur dioxide in alcohol solution gave colourless needles, m. p. 91—92° (Found: C, 25·7; H, 1·4; 2 mg. gave 3·61 mg., 3·68 mg. AgCl + AgBr. Calc. for $C_6H_3OClBr_2$: C, 25·1; H, 1·05%; AgCl + AgBr, 3·63 mg.), of 4-chloro-2 : 6-dibromophenol.

2-*Chloro*-2 : 4 : 6-*tribromo*-1 : 3-*dimethyl*cyclo*hexa*-3 : 6-*diene*-5-*one* (VI).—Chlorine (8 g.; 1 mol.) was introduced into a solution of 2 : 4 : 6-tribromo-*m*-5-xylenol (40 g.; 1 mol.) in acetic acid (800 c.c.) during 2 hours, at below 30°. On adding the mixture to water, a pale yellow precipitate separated, but this decomposed quickly when collected and dried; crystallisation then yielded a trihalogeno-*m*-5-xylenol in almost colourless needles, m. p. 164°. The crude wet *product* was dissolved immediately in light petroleum at 30—40°, the aqueous layer separated, and the solvent dried. Air was passed over the surface to remove the solvent, and the residue was crystallised quickly from dry light petroleum from which it separated in colourless plates, m. p. 120—122° (Found: C, 25·7; H, 1·7; total halogen, 69·15. $C_8H_6OClBr_3$ requires C, 24·4; H, 1·5; total halogen, 70·0%). Removal of halogen by sulphur dioxide–alcohol gave colourless needles, m. p. 164° (Found: C, 28·7; H, 2·0; total halogen, 63·9; 10·66 mg. gave 16·90 mg. of AgCl + AgBr. Calc. for $C_8H_5OClBr_2$: C, 30·5; H, 2·2; total halogen, 62·2%; AgCl + AgBr, 17·61 mg.), mainly of 2-chloro-4 : 6-dibromo-*m*-5-xylenol.

2 : 2 : 4-*Trichloro*-6-*bromo*-1 : 3-*dimethyl*cyclo*hexa*-3 : 6-*diene*-5-*one* (VII).—Chlorine (2·5 g.; 2·5 mols.) was introduced rapidly into a solution of 2 : 4 : 6-tribromo-*m*-5-xylenol (5 g.) in acetic acid (200 c.c.) at 10°. Next day the mixture was poured on ice–water and the precipitate treated as described in the previous experiment. Large, very pale yellow rectangular prisms, m. p. 105°, separated (Found: C, 31·2; H, 2·05; total halogen, 62·1; 10·997 mg. gave 21·95 mg. of AgCl + AgBr. $C_8H_4OCl_3Br$ requires

C, 31·5; H, 2·0; total halogen, 61·25%; AgCl + AgBr, 22·31 mg.), which are moderately stable when pure, although the crude *product* decomposes readily. Removal of labile halogen gave colourless needles, m. p. 165—166° (Found: C, 35·1; H, 2·6; total halogen, 55·5; 12·21 mg. gave 21·26 mg. of AgCl + AgBr. Calc. for $C_8H_7OCl_3Br$: C, 35·55; H, 2·6; total halogen, 55·9%; AgCl + AgBr, 21·48 mg.), not depressed on admixture with 2 : 4 : 6-tribromo- (m. p. 165—166°), 2-chloro-4 : 6-dibromo- (m. p. 164°), or 2 : 6-dichloro-4-bromo-*m*-5-xylenol (m. p. 165—166°); analyses, however, supported the last-named constitution.

2 : 4 : 6-*Trichloro*-m-5-*xylenol Bromide* (VIII).—Bromine (8 g.; 1·4 mols.) in acetic acid (20 c.c.) was added to 2 : 4 : 6-trichloro-*m*-5-xylenol (8 g.) in the same solvent (300 c.c.) at 60°. The mixture was heated to 110° for 2 minutes, and then kept at room temperature overnight. After addition of water, the pale yellow precipitate was filtered off and dissolved immediately in light petroleum and the aqueous layer separated. Removal of part of the solvent by air, followed by cooling at 0°, gave long, yellow plates of the *bromide*, m. p. 112°, unchanged on crystallisation from dry light petroleum. In air it decomposed rapidly with evolution of bromine, and it was analysed immediately (Found: 0·1418 g. gave 0·2865 g. of AgCl + AgBr. $C_8H_6OCl_3Br$ requires AgCl + AgBr, 0·2880 g.). On boiling it with alcohol, 2 : 4 : 6-trichloro-*m*-5-xylenol separated.

Chlorination of 4 : 6-*Dichloro*-2-*bromo*-m-5-*xylenol*. *Preparation of* 2 : 2 : 4 : 6-*Tetrachloro*-1 : 3-*dimethyl*cyclo*hexa*-3 : 6-*diene*-5-*one*.—Chlorine (3·2 g.; 1·2 mols.) was introduced into a solution of 4 : 6-dichloro-2-bromo-*m*-5-xylenol (10 g.) in acetic acid (250 c.c.) at 40—50°. Next day, after addition to water, the resulting precipitate was crystallised from light petroleum to give crystals, m. p. 70—90°. On allowing a solution in light petroleum to evaporate slowly during three weeks, a mixture of large, almost colourless, hexagonal prisms, m. p. 107—108° (approximately 4 parts) and a smaller amount of long, colourless, rectangular prisms, m. p. 106—107° (1 part) was separated by hand. A mixture of the two compounds melted at 70—90°. The former compound, m. p. 107—108°, was 2 : 2 : 4 : 6-tetrachloro-1 : 3-dimethyl*cyclo*hexa-3 : 6-diene-5-one (Found: C, 36·6; H, 2·3; total halogen, 54·1; 15·15 mg. gave 33·13 mg. AgCl + AgBr. Calc. for $C_8H_6OCl_4$: C, 36·9; H, 2·3; total halogen, 54·6%; AgCl + AgBr, 33·45 mg.), but the constitution of the substance, m. p. 106—107° (Found: C, 24·9; H, 1·65; total halogen, 68·6%; 12·12 mg. gave 28·58 mg. of AgCl + AgBr), was not established. It was stable to sulphur dioxide in aqueous alcohol.

4 : 5 : 6-*Tribromo*-m-2-*xylenol Bromide* (X).—4 : 5 : 6-Tribromo-*m*-2-xylenol (7·2 g.; 1 mol.) was added to a mixture of bromine (6·7 g.; 2·1 mols.) and water (150 c.c.); partial solution in the bromine layer was accompanied by reaction to give a solid mass. Crystallisation from dry ether gave very pale yellow prisms of the *compound*, m. p. 139—140° (yield, 7·5 g.; 85·3%) [Analysis (immediately): Found: Br, 73·3. $C_8H_6OBr_4$ requires Br, 73·05%]. Decomposition by boiling alcohol, and more readily by sulphur dioxide in alcohol, yielded 4 : 5 : 6-tribromo-*m*-2-xylenol; heating with zinc dust and water gave the same compound with some 4 : 5-dibromo-derivative. Compound (X) and boiling aqueous potassium iodide gave scarlet needles, m. p. 156—158° (from light petroleum), of the adduct of 4 : 6-dibromo-*m*-xyloquinone (1 mol.) and 4 : 5 : 6-tribromo-*m*-2-xylenol (2 mols.); the adduct was identical with a synthetic specimen, obtained by melting the two constituents and crystallising the product from chloroform.

4 : 5 : 6-*Tribromo*-m-2-*xylenol Chloride*.—4 : 5 : 6-Tribromo-*m*-2-xylenol (12 g.; 1 mol.) in acetic acid (75 c.c.) was mixed with chlorine (5 g.; 2·1 mols.) in the same solvent (75 c.c.), and a crystal of iodine added. After being warmed at 60° for 2 minutes, the mixture was kept at room temperature for 2 hours and poured on ice, and 15% aqueous sodium hydroxide (200 c.c.) was added; the resulting solid *product* crystallised from light petroleum in yellow prisms, m. p. 60—61° (Found: 0·0744 g. gave 0·137 g. of AgCl + AgBr. $C_8H_6OClBr_3$ requires 0·1338 g. AgCl + AgBr), decomposed to 4 : 5 : 6-tribromo-*m*-2-xylenol on prolonged boiling with alcohol, or to the same tribomo-compound with some 4 : 5-dibromo-*m*-2-xylenol, with zinc dust and water.

The authors thank Imperial Chemical Industries (Dyestuffs) Limited for gifts of chemicals.

CLOTHWORKERS' RESEARCH LABORATORY,
THE UNIVERSITY, LEEDS.

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90. *Acid–Base Catalysis in Non-aqueous Solvents. Part XI. The Halogenation of Acetone by Various* N*-Halogen Compounds in Chlorobenzene Solution at 50°.*

By R. P. BELL and A. D. S. TANTRAM.

Kinetic measurements have been made on the halogenation of acetone by three *N*-halogen compounds in chlorobenzene solution at 50°. The reaction is catalysed by acid and has an order between zero and unity with respect to the halogenating agent. A mechanism is proposed in which the acid catalyses the conversion of acetone into the enol form, and the enol is then halogenated, the two stages having comparable speeds. The experimental results agree quantitatively with this mechanism. It is shown that the reaction cannot involve acyl hypohalite as a halogenating reagent, as has been proposed by Israel, Tuck, and Soper (*J.*, 1945, 547) for some similar reactions.

REACTION with halogens has been widely used as a means of studying the prototropy of ketones and similar substances in aqueous solutions, the reactions being normally of zero order with

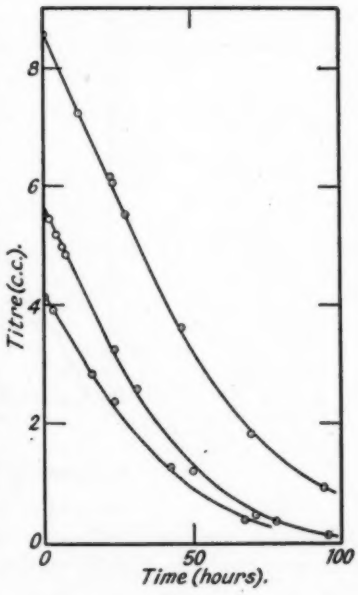
respect to halogen and catalysed by acids and bases. It is not possible to extend this method directly to non-dissociating solvents, since the halogen acids produced by halogenation act as immensely powerful catalysts (much more so than the hydrogen ions into which they are converted in aqueous solution). As a result the reaction becomes highly autocatalytic and even explosive in character. It was thought that the use of *N*-halogen compounds as halogenating agents might obviate these difficulties, since they bring about halogenation without the liberation of halogen acid. The present paper deals with the acid-catalysed halogenation of acetone in chlorobenzene solution.

Experimental.

Materials.—Acetone was purified through the sodium iodide compound. Chlorobenzene was dried over phosphoric oxide and redistilled. Monochloroacetic acid was an " AnalaR " product dried over calcium chloride in a desiccator.

It was necessary that the *N*-halogen compounds used should be stable, soluble, and free from basic or acidic groups. The three following compounds were finally selected, the percentage purities given referring to the quantity of iodine liberated from acidified potassium iodide solution. *N* : 2 : 4-Trichlorobenzanilide (I) was recrystallised twice from hexane, m. p. 86°, 99·7% pure; *NN'*-dichloro-*NN'*-di-(2 : 4 : 6-trichlorophenyl)urea (II) had m. p. 190° (decomp.), 99·2% pure; *N*-bromophthalimide (III) was recrystallised twice from benzene; m. p. 206°, 98·1% pure.

Fig. 1.



Kinetic Measurements.—The course of the reaction was followed by running samples of the reaction mixture into acid potassium iodide solution and titrating the liberated iodine. Preliminary experiments showed a fall in titre in solutions containing acetone, monochloroacetic acid, and *N*-halogen compound, but no such fall in solutions containing *N*-halogen compound together with acetone or monochloroacetic acid singly. Since acetone was always present in large excess, it was difficult to identify halogenated acetones, but the fate of the *N*-halogen compound could be determined by pouring into water and examining the solid precipitated. For example, a solution of (I) in excess of acetone gave after complete reaction an almost quantitative yield of white solid, m. p. 115°, undepressed by an authentic specimen of 2 : 4-dichlorobenzanilide. This confirms the fact that the reaction consists of the halogenation of the acetone rather than its condensation with the *N*-halogen compound.

The measurements were carried out at 50° in reaction vessels of the type previously described (Bell and Levinge, *Proc. Roy. Soc.*, 1935, **151**, *A*, 211) covered with tin-foil. Preliminary experiments showed that the reaction velocity is approximately proportional to the acetone concentration, and all the experiments recorded here refer to a fixed acetone concentration of 1·23M. Weighed samples of about 1 g. were taken, and the liberated iodine titrated with N/80-thiosulphate (micro-burette). Saturation of the chlorobenzene solution with water was found to have no effect on the reaction velocities, and no special precautions were therefore taken to exclude moisture.

The plots of titre against time were linear over a considerable part of their course, but approximated to a first-order change towards the end. Examples are given in Fig. 1. The tables below give, for each reaction, x_0, the initial concentration of *N*-halogen compound (in g.-equiv. of oxidising power per l.); the initial slope s (in g.-equiv. l.$^{-1}$ hr.$^{-1}$), taken from the linear part of the plot; and $t_{\frac{1}{2}}$, the time (in hours) required to reduce the concentration of *N*-halogen compound to one half. Only a few experiments were done with compound (III) : these gave results almost identical with those for (I), and have therefore not been recorded.

Compound (I).

$[CH_2Cl{\cdot}CO_2H] = 0{\cdot}0072$.

$100x_0$	2·22	5·00	5·68	7·60	10·14	15·12
10^4s	3·54	6·08	6·39	7·42	7·69	8·66
$t_{\frac{1}{2}}$	32·0	41·0	44·5	51·0	63·0	87·5

$[CH_2Cl{\cdot}CO_2H] = 0{\cdot}0138$.

$100x_0$	0·85	1·47	3·01	4·58	6·18	7·11	9·47	13·30	15·67
10^4s	2·83	3·11	6·21	8·71	11·1	9·41	11·4	13·8	14·9
$t_{\frac{1}{2}}$	19·5	23·4	24·2	27·0	28·0	38·2	41·5	48·0	52·5

Compound (II).

$[CH_2Cl{\cdot}CO_2H] = 0{\cdot}0072$.

$100x_0$	3·37	5·46	6·90	10·45	17·55
10^4s	7·6	9·4	9·5	11·4	11·7
$t_{\frac{1}{2}}$	20·0	29·0	36·5	46·0	76·0

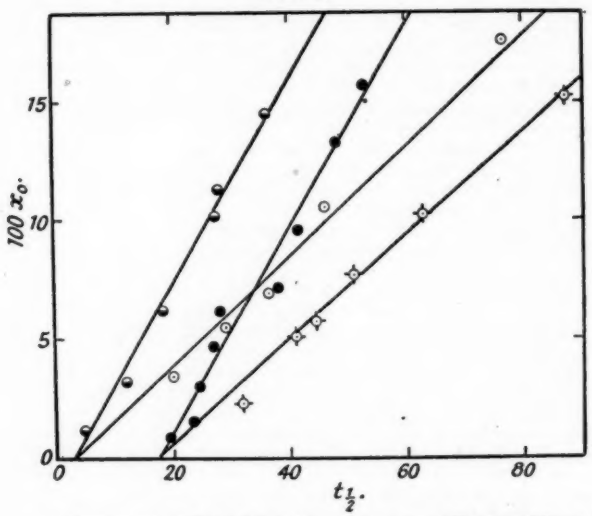
$[CH_2Cl{\cdot}CO_2H] = 0{\cdot}0138.$

$100x_0$	1·28	3·26	6·16	10·11	11·32	14·54
10^4s	11·6	13·4	16·5	18·4	20·5	20·5
$t_{\frac{1}{2}}$	4·9	12·2	18·5	27·5	28·0	36·1

Discussion.

The halogenation of acetone under our conditions is clearly catalysed by acids, but the reaction is not of zero order with respect to the halogenating agent. The shape of the curves in Fig. 1 and the variation of s and $t_{\frac{1}{2}}$ with the initial concentrations of (I) and (II) suggest a reaction order intermediate between unity and zero. This can be explained by supposing that the acetone is first enolised in presence of the acid catalyst, and the enol then halogenated by the

Fig. 2.



⊹=Compound I, 0·0072 M-acid. ⊙=Compound II, 0·0072 M-acid.
●= " " 0·0138 M-acid. ⊖= " " 0·0138 M-acid.

N-halogen compound, the two steps being of comparable rates. Schematically if K and E represent the keto- and the enol form of acetone, N the N-chloro-compound, and BH the acid, then

$$K + BH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E + BH$$

$$E + N \xrightarrow[k_2]{} \text{products}$$

giving for a stationary concentration of E

$$-\frac{d[N]}{dt} = \frac{k_1k_2[K][BH][N]}{k_{-1}[BH] + k_2[N]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

During the course of a given reaction [BH] is constant and [K] sensibly so; hence this equation can be integrated. Writing $[N] = x$ this gives

$$t = \alpha \log x_0/x + \beta(x_0 - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and in particular

$$t_{\frac{1}{2}} = \alpha \log 2 + \tfrac{1}{2}\beta x_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $\alpha = k_{-1}/k_1k_2[K]$, $\beta = 1/k_1[K][BH]$. The value of [K] was the same in all our experiments: hence in a series of experiments with the same N-halogen compound and the same acid concentration, the plot of $t_{\frac{1}{2}}$ against x_0 should give a straight line. Fig. 2 shows four such plots for the four series in the table. Moreover, since k_{-1}/k_1 is independent of the nature or concentration of the catalyst, the intercept α log 2 of these lines on the t axis should depend only on the nature of the N-halogen compound, and the slopes $\frac{1}{2}\beta$ should depend only on the acid concentration. Both of these points are confirmed by the plots in Fig. 2. Finally, the slopes

should be inversely proportional to the acid concentration; the ratio of the slopes for the two sets of lines in Fig. 2 is 1·93, exactly equal to the inverse ratio of the two acid concentrations.

A similar test may be made in terms of the initial rates s. Equation (1) gives

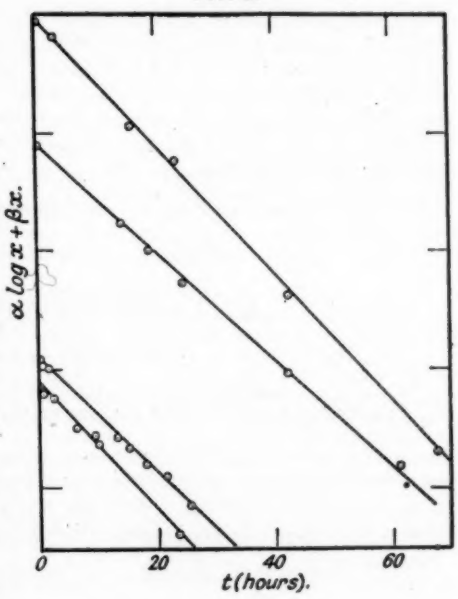
$$1/s = \alpha/x_0 + \beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

leading to plots of $1/s$ against $1/x_0$ similar to those in Fig. 2.

We can also investigate whether the course of individual reactions corresponds to equation (2), using the values of α and β derived from Fig. 2. Fig. 3 shows plots of $\alpha \log x + \beta x$ against t for four typical experiments, with the scales displaced vertically for convenience. The slopes of the lines drawn are 0·98, 0·92, 1·10, and 1·06, compared with the theoretical values of unity.

The experimental data therefore accord well with the reaction scheme proposed, *i.e.*, an acid-catalysed enolization followed by halogenation of the enol. The relative reactivities of the two compounds (I) and (II) are proportional to the corresponding values of k_2 or $1/\alpha$, showing that (II) is about 4·4 times as reactive as (I), after allowing for the fact that (II) has two reactive chlorine atoms. The rate of enolization is measured by $1/\beta$ [*i.e.*, the limiting halogenation rate for an infinitely large value of x_0: cf. equation (4)], which is of course the same for both *N*-halogen compounds. For 0·0138M-monochloroacetic acid this rate works out at $1{\cdot}07 \times 10^{-3}$ mole of acetone/l./hour, in a solution containing 1·23M-acetone. Referred to unit concentrations of acid and acetone, this gives $k_1 = 0{\cdot}063$ mole/l./hour for the catalytic constant of monochloracetic acid for the enolization of acetone at 50°. It is of interest to note that this is identical with the value extrapolated from the data of Smith (*J.*, 1934, 1744) at 0° and 25° for the same catalytic constant in aqueous solution. On purely electrostatic grounds the value in chlorobenzene would be expected to be lower than that in water, but the position is likely to be complicated by the association of the carboxylic acid group with itself or with water (cf. Bell, " Acid-Base Catalysis ", p. 112, Oxford 1941).

FIG. 3.



Israel, Tuck, and Soper (*J.*, 1945, 547) have recently investigated the halogenation of anisole and its derivatives by various *N*-bromo-compounds. They find that bromination does not take place unless acetic acid is added to the solution, whereupon the reaction velocity is found to be independent of the nature and concentration of the anisole, but depends on the concentrations of acid and of *N*-bromo-compound. This is interpreted by supposing that the halogenating agent is the acyl hypohalite, the rate-determining step being the reaction

$$R{\cdot}CO_2H + {>}NX \longrightarrow R{\cdot}CO_2X + {>}NH$$

This step cannot be solely rate-determining in our work, since the reaction velocity was found to depend on the acetone concentration. It might, however, be suggested that the rôle of the acid is to form acyl hypohalite, and not to catalyse the formation of enol from the acetone. The reaction scheme then becomes

$$>NX + BH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} >NH + BX$$

$$BX + \text{acetone (K)} \xrightarrow[k_2]{} \text{products}$$

BX is the acyl hypohalite, which may be assumed to react either with the keto-form of acetone, or with the enol in equilibrium with it. The condition for a stationary concentration of BX gives

$$-\frac{dx}{dt} = \frac{k_1 k_2 x[BH][K]}{k_{-1}(x_0 - x) + k_2[K]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and on integration

$$t = (\alpha x_0 + \beta) \log x_0/x - \alpha(x_0 - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$t_{\frac{1}{2}} = (\alpha x_0 + \beta) \log 2 - \tfrac{1}{2}\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $\alpha = k_{-1}/k_1k_2[\mathrm{BH}][\mathrm{K}]$, $\beta = 1/k_1[\mathrm{BH}]$.

Like equation (3), (7) predicts that for a given *N*-halogen compound and a given acid concentration the plot of $t_{\frac{1}{2}}$ against x_0 should give a straight line of slope inversely proportional to the acid concentration. However, since k_1, k_{-1}, and k_2 now all depend on the nature of > NX, different halogenating agents should give different slopes, in contradiction to equation (3) and to experiment. Moreover, equation (7) predicts an intercept $\alpha \log 2 - \frac{1}{2}\beta$ inversely proportional to the acid concentration, while experiment gives intercepts independent of acid concentration, as demanded by equation (3). It is clear, therefore, that our results are not consistent with a reaction scheme in which the acid serves solely as a source of acyl hypohalite. There still remains the possibility that it acts both as an acid catalyst for enolisation and as a source of acyl hypohalite. However, if this were so, the velocity for low concentrations of *N*-halogen compound > NX (where the halogenation rate largely determines the observed velocity) should be decreased by adding an excess of the compound > NH, owing to repression of the reaction $> \mathrm{NX} + \mathrm{R{\cdot}CO_2H} \rightleftharpoons \mathrm{R{\cdot}CO_2X} + > \mathrm{NH}$. In order to test this, a 20-fold excess of 2 : 4-dichlorobenzanilide was added in an experiment with 0·007N-*N* : 2 : 4-trichlorobenzanilide. The result was to increase the velocity threefold, probably because of basic catalysis by the > NH group. It therefore seems very improbable that acyl hypohalite plays any part in the reaction.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, April 10th*, 1947.]

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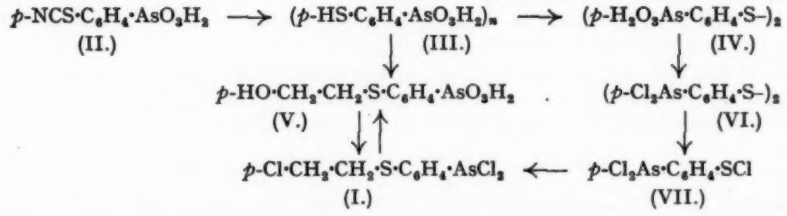
91. p-(2-*Chloroethylthio*)*phenyldichloroarsine.*

By H. T. OPENSHAW and A. R. TODD.

The substance named in the title has been synthesised from *p*-arsanilic acid by two methods. It possesses relatively mild vesicant properties.

IN the course of a series of investigations on potential new chemical warfare agents, it was considered of interest to prepare p-(2-*chloroethylthio*)*phenyldichloroarsine* (I), which combines in its molecule structural features of the known vesicants phenyldichloroarsine and 2 : 2′-dichlorodiethyl sulphide. The substance proved to be a weaker vesicant than either of these compounds.



The preparation of *p*-thiocyanatophenylarsonic acid (II) from *p*-arsanilic acid, and its conversion into polymeric *p*-mercaptophenylarsonic acid (III) and thence into diphenyldisulphide *pp′*-diarsonic acid (IV) were carried out essentially by the methods described by Barber (*J.*, 1930, 2727). The mercapto-acid (III) reacted smoothly in alkaline solution with ethylene chlorohydrin, and the resulting *p*-(2-hydroxyethylthio)phenylarsonic acid (V) on treatment with concentrated hydrochloric acid and sulphur dioxide yielded the desired substance (I). An alternative method of synthesis involved the reduction of the disulphide acid (IV) to *diphenyldisulphide*-pp′-*bis*(*dichloroarsine*) (VI). Treatment of a chloroform solution of (VI) with chlorine gave a solution containing *p*-dichloroarsinophenylsulphenyl chloride (VII), which reacted with ethylene to yield (I). The identity of the product obtained by the second method was established by its conversion into the acid (V) by means of iodine and aqueous sodium hydrogen carbonate.

The work described in this paper was carried out in 1941. Simultaneously and

independently, Morgan and Hamilton carried out a similar investigation, the results of which were transmitted to us after our work was complete. Subsequently, Morgan and Hamilton published their preparation of the acid (V) (*J. Amer. Chem. Soc.*, 1944, **66**, 874), but publication of our work was withheld for security reasons.

Experimental.

p-*Thiocyanatophenylarsonic Acid* (II).—The directions given by Barber (*loc. cit.*) were followed, with the exception that the addition of diazotised arsanilic acid to the cuprous thiocyanate was made in portions and the vigorous foaming which occurred was controlled by addition of a little capryl alcohol. The yield of recrystallised product was 50% (Barber claims 30%) (Found : neutralisation equiv., 129·5. Calc. for $C_7H_4O_2NSAs$: equiv., 129·5).

p-(2-*Hydroxyethylthio*)*phenylarsonic Acid* (V).—*p*-Thiocyanophenylarsonic acid (50 g.) was dissolved in 10% aqueous sodium hydroxide (500 c.c.) and the solution refluxed for 6 hours. The hot solution was acidified (Congo-red), and after several hours the crude *p*-mercaptophenylarsonic acid (III) (36·4 g.; 80%), an orange amorphous powder, was collected, washed with water, and dried at 60°.

The above crude mercapto-acid (30 g.) was dissolved in a solution of sodium hydroxide (16 g.) in water (400 c.c.), and ethylene chlorohydrin (9 c.c.) added. After standing at room temperature for 18 hours, the mixture was heated on the steam-bath for 2 hours. The hot solution was acidified (Congo-red), and on cooling the product (32·5 g.; 91%) crystallised. Recrystallisation from water gave nearly colourless leaflets (29·5 g.), m. p. 118° (Found : C, 34·1; H, 4·0; S, 11·2. Calc. for $C_8H_{11}O_4SAs$: C, 34·5; H, 4·0; S, 11·5%). The substance is dimorphous, and on crystallisation from dilute hydrochloric acid (5%) it usually separated in needles, m. p. 132—133°. From an aqueous solution needles or leaflets can be obtained by seeding with the appropriate form. The properties agree with those described by Morgan and Hamilton (*loc. cit.*).

Diphenyldisulphide-pp′-*diarsonic Acid* (IV).—Crude *p*-thiophenylarsonic acid (30 g.) was suspended in saturated aqueous sodium hydrogen carbonate (250 c.c.) and treated with the calculated volume (128 c.c.) of N-iodine. Excess of iodine is to be avoided, as oxidation proceeds further, though at a slower rate. When reaction was complete, the solution (filtered if necessary) was heated to boiling and just acidified to Congo-red. After cooling, the crystalline disulphide (27·5 g.; 92%) was collected, washed with water, dried and recrystallised from 50% aqueous acetic acid. It formed nearly colourless leaflets (24 g.), m. p. 220° (decomp.) (Found : C, 30·3; H, 2·7. Calc. for $C_{12}H_{12}O_6S_2As_2$: C, 30·9; H, 2·6%).

Diphenyldisulphide-pp′-*bis*(*dichloroarsine*) (VI).—Diphenyldisulphidediarsonic acid (10 g.) was dissolved in concentrated hydrochloric acid (50 c.c.) at room temperature. After a few minutes, crystallisation set in and the whole solution set to a thick paste. The colourless, crystalline material (11·25 g.) was collected on a sintered glass filter, washed with a little concentrated hydrochloric acid, and dried in a vacuum over sodium hydroxide. The substance is probably $(Cl_2OAs{\cdot}C_6H_4{\cdot}S{-})_2$; on treatment with hot water the original arsonic acid is produced. This oxychloride (10 g.) was suspended in concentrated hydrochloric acid (50 c.c.), chloroform (30 c.c.) and a trace of sodium iodide were added, and sulphur dioxide was passed into the mixture at room temperature, with occasional shaking, until the colour of iodine was discharged. The resulting pasty mixture was filtered, and the crystalline material was washed with a little cold chloroform and dissolved in boiling chloroform. The hot solution was dried ($CaCl_2$) and filtered; on cooling, colourless crystals of *diphenyldisulphide*-pp′-*bis*(*dichloroarsine*) (6 g.) separated. From the mother liquors and from the original chloroform washings a further quantity (1·9 g.) was obtained (total yield, 84%). The substance had m. p. 125·5—126·5° (Found : C, 28·8; H, 1·7; S, 13·0. $C_{12}H_8Cl_4S_2As_2$ requires C, 28·3; H, 1·6; S, 12·6%). When the reduction of the diarsonic acid was carried out without the intermediate isolation of the oxychloride, the yield was lower (65%).

p-(2-*Chloroethylthio*)*phenyldichloroarsine* (I).—(a) *By reduction of* p-(2-*chloroethylthio*)*phenylarsonic acid*. A solution of the arsonic acid (10 g.) in concentrated hydrochloric acid (50 c.c.) was heated on the steam-bath for 1 hour. A small amount of an oil separated from the hot solution, and on cooling a considerable oily layer separated. After addition of chloroform (20 c.c.) and a trace of sodium iodide, sulphur dioxide was passed in. The mixture became warm as reduction proceeded. When the colour of iodine had been discharged, the chloroform layer was collected and the aqueous layer extracted once with chloroform. The combined chloroform solutions were dried and evaporated, and the residual oil (10·6 g.; 96%) was distilled. p-(2-*Chloroethylthio*)*phenyldichloroarsine* was obtained as a colourless oil, b. p. 148—152°/0·05 mm. (7·75 g.; 68%) (Found : C, 30·8; H, 2·8; Cl, 32·2; S, 10·5. $C_8H_9Cl_3SAs$ requires C, 30·3; H, 2·5; Cl, 33·6; S, 10·1%). Titration of a chloroform solution with N/10-iodine in the presence of excess of aqueous sodium hydrogen carbonate required 98% of the calculated amount of iodine.

(b) *From diphenyldisulphide*-pp′-*bis*(*dichloroarsine*). The bis(dichloroarsine) (5 g.) was suspended in dry chloroform (50 c.c.), and a slow stream of dry chlorine was passed into the mixture at room temperature with occasional shaking. The solid gradually dissolved to give a bright yellow solution; when solution was complete, introduction of chlorine was stopped. The increase in weight of the solution was approximately 0·8 g. (theory, 0·71 g.). Excess of chlorine was removed by passing a stream of dry nitrogen through the liquid for 1½ hours. Ethylene was then passed in until the yellow colour of the solution was discharged and, very slowly, for a further hour. The chloroform was removed by distillation, leaving a brown oil (6 g.), from which a trace of crystalline material separated. The oil was taken up in chloroform, filtered, and distilled. The product (3·9 g.; 62%) had b. p. 144—152°/0·04 mm.; a redistilled sample, b. p. 152°/0·04 mm., gave poor analytical results (Found : C, 28·2; H, 2·5; Cl, 32·2%). That it consisted essentially of the required compound was, however, evident from its behaviour towards iodine; 0·1340 g. in chloroform and aqueous sodium hydrogen carbonate required 8·45 c.c. of 0·098N-iodine (calc., 8·6 c.c.), and after titration 4-(2-hydroxyethylthio)-

phenylarsonic acid was obtained from the aqueous layer by concentration and acidification. It had m. p. 118° undepressed in admixture with an authentic specimen.

These results are published with the permission of the Chief Scientist, Ministry of Supply, to whom our thanks are due.

THE UNIVERSITY, MANCHESTER. [*Received, April 21st*, 1947.]

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92. *Azlactones and Phenylacetic Acids derived from the 2-Nitro-derivatives of Vanillin, isoVanillin, and Veratraldehyde.*

By S. F. MACDONALD.

2-Nitro-3-hydroxy-4-methoxyphenylacetic acid, which should be a useful intermediate for the synthesis of such aporphine alkaloids as bulbocapnine, has been prepared from 2-nitro*iso*-vanillin *via* an intermediate azlactone. An improved method for preparing such azlactones also made 2-nitro-3-methoxy-4-hydroxyphenylacetic acid more readily available, and provided an alternative route to 2-nitro-3 : 4-dimethoxyphenylacetic acid.

OF the methods which might be applied to the preparation of *2-nitro-3-hydroxy-4-methoxyphenylacetic acid* from 2-nitro*iso*vanillin, that used in preparing 2-nitrohomoveratric acid *via* its nitrile (Kay and Pictet, *J.*, 1913, **103**, 947) involves the low yield of a Cannizzaro reaction, and an excellent modification (Slotta and Lauersen, *J. pr. Chem.*, 1934, **139**, 220) appears to be applicable only to the fully methylated derivatives, for we could not reduce 2-nitrovanillin acetate by the aluminium *iso*propoxide method. A second possibility was to proceed through the azlactone obtained by condensing the aldehyde with hippuric acid. This has been done with 2-nitrovanillin (Gulland, Ross, and Smellie, *J.*, 1931, 2885) and, as far as the phenylpyruvic acid, with 2-nitroveratraldehyde (Avenarius and Pschorr, *Ber.*, 1929, **62**, 321; Gulland, Robinson, Scott, and Thornley, *J.*, 1929, 2924). The yields of the azlactones were variable, and their hydrolysis to the phenylpyruvic acids difficult.

It was found that the aldehydes mentioned above may be condensed with aceturic or hippuric acid in the presence of acetic anhydride to give azlactones if the usual catalyst, sodium acetate, is replaced by triethylamine, and long reaction times at relatively low temperatures are employed. In this way pure products were obtained directly, and in good yield, regardless of the size of the run.

When aceturic acid was used, the *azlactones* obtained were easily hydrolysed to the pyruvic acids, from which the phenylacetic acids were obtained by oxidation in the usual manner. The preparation of 2-nitrohomovanillic acid from vanillin acetate proceeded very smoothly in 40% over-all yield, compared with a maximum of 15% by the earlier method (Gulland, Ross, and Smellie, *loc. cit.*). That of 2-nitro-3-hydroxy-4-methoxy- and of 2-nitro-3 : 4-dimethoxyphenylacetic acid went less smoothly. In the latter case, the yield was good, but the m. p. of the product could not be brought to the value recorded in the literature.

It was not found possible to replace aceturic acid by formylglycine, in the preparation of the azlactones, to facilitate further their hydrolysis.

It was observed by Gulland, Ross, and Smellie (*loc. cit.*) that crystallisation of azlactones from alcohol might result in rupture of the azlactone ring with the formation of acylamido-cinnamic esters. In this connection, we have observed that the azlactones obtained by condensing benzaldehyde or veratraldehyde with aceturic or hippuric acid were quantitatively converted into the acylamido-cinnamic esters by refluxing for about one hour with methyl or ethyl alcohol in the presence of (neutral) sodium acetate; without the acetate they were unchanged, and its catalytic action was inhibited by a little acetic acid.

The preparation of 2-nitroveratraldehyde was improved by methylating 2-nitrovanillin acetate directly, a method which was also applied to the benzylation of the latter.

EXPERIMENTAL.

2-Nitrovanillin Acetate.—Vanillin acetate was nitrated at − 5° to 0° (Pschorr and Somuleanu, *Ber.*, 1899, **32**, 3405) by fresh fuming nitric acid (*d* 1·59—1·60) with vigorous stirring. The crude product, after being washed with much cold water, was crystallised from acetic acid (2 parts)–water (0·5 part). In runs of 50—250 g., yields of 75—85% were obtained; m. p. 85°. The use of older acid decreased the yield to as low as 50%; weaker acids (*d* 1·50) resulted in oily products (cf. Gulland, Ross, and Smellie, *loc. cit.*).

The mother-liquors from the crystallisation sometimes deposited pale yellow plates, m. p. 121·5°,

identified as 6-nitrovanillin acetate by conversion into 6-nitrovanillin (Raiford and Stoesser, *J. Amer. Chem. Soc.*, 1928, **50**, 2556).

Azlactone of 2-Nitro-α-benzamido-3-methoxy-4-acetoxycinnamic Acid.—2-Nitrovanillin acetate (23·9 g.), hippuric acid (20 g.), acetic anhydride (30 c.c.), and triethylamine (10 c.c.) were mixed and kept in a stoppered flask at 25° for some hours, at 40° for 1 day, at 50° for 2 days, and at 0° for 1 day. The azlactone was then filtered off, washed with alcohol and with water, and crystallised from acetic acid containing acetic anhydride, giving yellow plates (21·7 g., 61%), m. p. 171·5—172·5° (Gulland, Ross, and Smellie, *loc. cit.*, found m. p. 171—172°).

Azlactone of 2-Nitro-α-acetamido-3-methoxy-4-acetoxycinnamic Acid.—2-Nitrovanillin acetate (47·8 g.), aceturic acid (25 g.), and acetic anhydride (50 c.c.) were mixed, and triethylamine (20 c.c.) added, a rise in temperature being avoided. The mixture was kept in a stoppered flask at 20° for 1 day, at 40° for 6 days, at 55° for 1 day, then at 0° for 2 days. The *azlactone* was then filtered off and washed with cold 75% alcohol (200 c.c.) and with hot water, giving yellow needles (39·5 g., 62%), m. p. 130°. Crystallised from acetic acid containing acetic anhydride, it had m. p. 131° (Found: N, 8·25. $C_{14}H_{12}O_7N_2$ requires N, 8·75%).

2-Nitro-4-hydroxy-3-methoxyphenylpyruvic Acid.—The crude azlactone of 2-nitro-α-acetamido-4-hydroxy-3-methoxycinnamic acid (10 g.) was refluxed with water (90 c.c.) and hydrochloric acid (10 c.c.) for 2½ hours; during the first ½ hour the mixture was frequently shaken, and the lumps broken up to bring about rapid solution. The solution was then cooled, water (50 c.c.) and 40% aqueous sodium hydrogen sulphite (45 c.c.) added, and the solution saturated with sulphur dioxide and extracted three times with ether. The aqueous layer, containing some crystalline solid matter, was treated with hydrochloric acid (20 c.c.) and evaporated in a vacuum nearly to dryness. Extraction of the residue with ethyl acetate, distillation of the solvent from the extract, and washing of the product on to the filter with benzene gave 7·08 g. (88%), m. p. 180—181° (Gulland, Ross, and Smellie, *loc. cit.*, found 182°).

2-Nitro-4-hydroxy-3-methoxyphenylacetic Acid.—The above phenylpyruvic acid was dissolved in cold N-sodium hydroxide (100 c.c.), and 30% hydrogen peroxide (3·6 c.c.) added at 0—10°. After the mixture had been left overnight at 0°, saturation with sulphur dioxide gave the product as yellow plates (5·57 g.), m. p. 159·5—160·5°. The mother-liquors gave 0·17 g., m. p. 158—159°, by extraction with ethyl acetate and crystallisation of the residue, left on removing the solvent, from water (8 c.c.) (charcoal); total yield, 91%. For analysis it was crystallised from 10 parts of water, giving thick, pale yellow, hexagonal plates, m. p. 159·5—160·5° (Gulland, Ross, and Smellie, *loc. cit.*, gave 161°) (Found: N, 6·1. Calc. for $C_9H_9O_6N$: N, 6·2%).

Benzyl Ether of 2-Nitrovanillin.—A mixture of 2-nitrovanillin acetate (12 g.), powdered sodium hydrogen carbonate (8·5 g.), benzyl chloride (6 c.c.), and methanol (60 c.c.) was refluxed for 5 hours, then most of the methanol was distilled off. Water (100 c.c.) and 50% aqueous sodium hydroxide (15 c.c.) were added, the mixture was shaken at 80°, cooled, shaken with light petroleum, and the *benzyl ether* filtered off. After being washed with water and light petroleum, and crystallised from acetic acid–water, it was obtained as colourless plates (7 g.), m. p. 111—112°. For analysis it was recrystallised from acetic acid; m. p. 111·5—112·5° (Found: C, 62·8; H, 4·3. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·6%).

Azlactone of 2-Nitro-α-acetamido-4-benzyloxy-3-methoxycinnamic Acid.—The benzyl ether of 2-nitrovanillin (5 g.), aceturic acid (2·5 g.), acetic anhydride (7 c.c.), and triethylamine (2 c.c.) were mixed and kept in a stoppered flask for 1 day at 25°, for 2 days at 40°, and for successive one-day periods at 50°, 60°, 70°, 80°, and 0°. The *azlactone* was then filtered off and washed with 95% alcohol, giving 4·5 g. (70%), m. p. 163—164°. Recrystallisation from acetic acid containing acetic anhydride gave thick yellow needles, m. p. 163·5—164·5° (Found: N, 7·3. $C_{19}H_{16}O_6N_2$ requires N, 7·6%).

iso*Vanillin.*—The following method is an improvement upon recorded methods. Protocatechuic aldehyde (*Org. Synth.*, **18**, 75) (100 g. of the crude product) was stirred in water (2 l.) held at 80° in a 4-l. beaker. Sodium hydrogen carbonate (70 g.) was then added, followed by methyl sulphate (60 c.c.) in four portions. The alternate addition of sodium hydrogen carbonate (63 g.) and of methyl sulphate (60 c.c.) was then repeated three times, each pair of additions requiring about 6 minutes; the pH fluctuated between 7 and 8. The mixture was then cooled, and the product filtered off. The mother-liquor was then methylated at 80° as above with three lots of the bicarbonate and of methyl sulphate, and cooled, salt (400 g.) added, and the mixture extracted with ether (500 c.c.). The ether and the product previously filtered off were shaken together with 10% aqueous sodium hydroxide (450 c.c.). Addition of salt (100 g.) to the aqueous layer, cooling, and adjustment of the pH to 6, precipitated *iso*vanillin (46 g.) which, after 2 crystallisations from water (charcoal), gave 35 g., m. p. 114—115°.

The ethereal layer gave veratraldehyde (43 g.) from which more *iso*vanillin was obtained by demethylation (Robinson and Sugasawa, *J.*, 1931, 3167).

2-Nitroisovanillin.—This was prepared by Pschorr and Stohrer's method (*Ber.*, 1902, **35**, 4393). No better results were obtained by nitrating *iso*vanillin in various solvents with acetyl nitrate, benzoyl nitrate, or anhydrous nitric acid.

Azlactone of 2-Nitro-α-acetamido-3-acetoxy-4-methoxycinnamic Acid.—2-Nitroisovanillin (20 g.), acetic anhydride (40 c.c.), and powered aceturic acid (14 g.) were mixed, and triethylamine (10 c.c.) added, the temperature being held below 30°. The flask containing the mixture was stoppered and heated for 2 days at 37°, then for five days at 50°, then kept at 0° for two days. The *azlactone* was filtered off, slurried, and washed with cold 50% alcohol (110 c.c.), giving 19·7 g. (61%) as a light orange powder, m. p. 198°. Recrystallised twice from five parts of acetic acid–acetic anhydride (4 : 1), it formed orange prisms, m. p. 199·5—200·5° (Found: C, 52·5; H, 3·8; N, 8·6. $C_{14}H_{12}O_7N_2$ requires C, 52·5; H, 3·8; N, 8·75%).

2-Nitro-3-hydroxy-4-methoxyphenylpyruvic Acid.—The foregoing crude azlactone (5 g.) was refluxed for 2½ hours with water (45 c.c.) and hydrochloric acid (5 c.c.), the mixture being shaken and the lumps broken up occasionally during the first ½ hour until the solid had dissolved. Sodium hydrogen sulphite (25 c.c. of a 40% solution) was added, and the solution cooled and extracted three times with ether.

The aqueous layer was treated with hydrochloric acid (12 c.c.), shaken under vacuum until frothing ceased, boiled in a current of carbon dioxide, then distilled in a vacuum to dryness. The solid was extracted with ethyl acetate, which on evaporation left the required *acid* (3·8 g.). Crystallisation from acetic acid gave plates, m. p. 168·5—169° (Found: N, 5·5. $C_{10}H_9O_7N$ requires N, 5·5%).

2-Nitro-3-hydroxy-4-methoxyphenylacetic Acid.—The crude pyruvic acid (above) was dissolved in 6·6% sodium hydroxide (33 c.c.), and hydrogen peroxide (2 c.c. of 30%) added at 0°. After standing for a day at 0°, the *product* (2·4 g.) was precipitated by sulphuric acid. After four recrystallisations from water (25 c.c.) (charcoal), it was obtained as yellow plates (1·15 g., 33%), m. p. 166—167° (Found: C, 47·6; H, 4·1; N, 6·2. $C_9H_9O_6N$ requires C, 47·6; H, 4·0; N, 6·2%).

2-Nitroveratraldehyde.—2-Nitrovanillin acetate (150 g.), water (600 c.c.), and methyl sulphate (250 c.c.) were mixed and stirred vigorously while 50% aqueous sodium hydroxide (100 c.c.) was added dropwise during one hour, the pH being kept at about 8 and the temperature at 35—40° throughout. Methyl sulphate (125 c.c.) was then added, and more alkali (100 c.c.) as before, but the last 50 c.c. were added to keep the pH at about 11. After 20 minutes' more stirring, the mixture was made alkaline, cooled, ice and ammonia added, and the whole left at 0°. The product was filtered off, washed with water (3 l.), and crystallised from acetic acid (385 c.c.)–water (250 c.c.); more was obtained by recrystallising a second crop obtained by diluting the mother-liquors; yield, 114 g. (86%), m. p. 63·5—64°.

Azlactone of 2-Nitro-α-acetamido-3 : 4-dimethoxycinnamic Acid.—2-Nitroveratraldehyde (84·4 g.), aceturic acid (50 g.), and acetic anhydride (100 c.c.) were mixed, and triethylamine (40 c.c.) added, a rise in temperature being avoided. The flask was stoppered, and the mixture kept for successive one-day periods at 25°, 40°, 60°, 80°, and 0°. The *azlactone* was then filtered off and washed with cold 50% alcohol (250 c.c.) then with water, giving 87·5 g. (75%), m. p. 199°. Recrystallisation from acetic acid containing acetic anhydride gave yellow needles, m. p. 201° (Found: C, 53·6; H, 4·0; N, 9·5. $C_{13}H_{12}O_6N_2$ requires C, 53·4; H, 4·1; N, 9·6%).

2-Nitro-3 : 4-dimethoxyphenylpyruvic Acid.—To the foregoing crude azlactone (12 g.) and dioxan (50 c.c.), water (500 c.c.) was added, and the mixture refluxed for 1 hour. Hydrochloric acid (50 c.c.) was then added, and refluxing continued for 2½ hours. The mixture was frequently shaken throughout. It was then filtered hot (charcoal). Cooling precipitated most of the crude product; the remainder was extracted with ether after saturation of the mother-liquor with salt. The ether and then the solid were extracted with 2N-sodium hydroxide (130 c.c.), and the alkaline solution treated with 40% sodium hydrogen sulphite (15 c.c.), saturated with sulphur dioxide, extracted three times with ether, hydrochloric acid (35 c.c.) added, and sulphur dioxide removed in a vacuum on the water-bath. After cooling, the pale yellow plates (8 g., 72%) were filtered off, m. p. 177° (Avenarius and Pschorr, *loc. cit.*, gave 172°) (Found: N, 4·9. Calc. for $C_{11}H_{11}O_7N$: N, 5·2%).

2-Nitro-3 : 4-dimethoxyphenylacetic Acid.—The foregoing crude acid (8 g.) in N-sodium hydroxide (110 c.c.) was oxidised with 30% hydrogen peroxide (4 c.c.) below 10°. Sulphur dioxide precipitated colourless plates (6·8 g., 95%), m. p. 143°. Repeated crystallisation from water, attended by considerable losses, did not raise the m. p. above 145° (Slotta and Lauersen, *loc. cit.*, give 146°) (Found: C, 49·8; H, 4·4. Calc. for $C_{10}H_{11}O_6N$: C, 49·8; H, 4·6%).

BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH,
UNIVERSITY OF TORONTO, TORONTO, CANADA.

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93. *A Contribution to the Chemistry of the Inner Complex Salts of Dimethylglyoxime.*

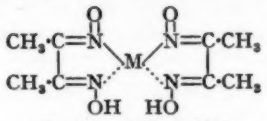
By FRITZ FEIGL and HANS A. SUTER.

The constitution of various complexes of metals with dimethylglyoxime is discussed, and in particular a ferrous complex formerly supposed to be (II). Thilo and Friedrich had shown that both the oximino-groups of dimethylglyoxime are capable of entering into complex formation, and this is now further demonstrated by the preparation of several salts of dimethylglyoxime-palladium acid, $H_2[Pd(C_4H_6O_2N_2)_2]$.

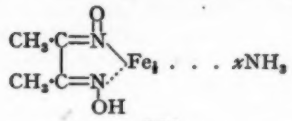
SINCE Tschugaeff (*Ber.*, 1905, **38**, 2520) published the first of his papers on the insoluble red nickel salt of dimethylglyoxime, about 150 publications have appeared on the analytical applications of 1 : 2-dioximes (see Diehl, "The Applications of the Dioximes in Analytical Chemistry", Columbus, Ohio, 1940) and on the constitution of their metal derivatives. The water-insoluble nickel and palladium compounds of dimethylglyoxime are of special interest. They are usually regarded as inner complex compounds and represented as shown in (I). This structure was fairly well validated by the experimental studies of Pfeiffer (*Ber.*, 1930, **63**, 1811). Tschugaeff and Orelkin (*Z. anorg. Chem.*, 1914, **89**, 401) described the preparation of a water-soluble ferrous compound of dimethylglyoxime; it results when dimethylglyoxime and ammonia are added to a tartrated ferrous solution. The compound, which is readily oxidized, has hitherto been written as in (II), *i.e.*, as an inner complex salt with co-ordinated ammonia molecules.

An examination of the structural formulæ (co-ordination formulæ) (I) and (II) reveals that

only one of the two oximino-groups is capable of direct salt formation. The other is bound co-ordinatively to the metal atom, *i.e.*, by auxiliary valencies emanating from the nitrogen atom.



(I; M = Ni or Pd.)

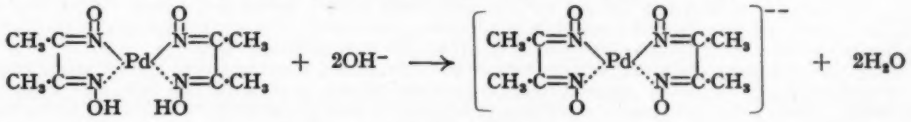


(II.)

Thilo and Friedrich (*Ber.*, 1929, **62**, 2998) were the first to obtain evidence that both these groups of dimethylglyoxime can function as salt-formers. They treated nickel dimethylglyoxime with sodium ethoxide in absolute alcohol and thus produced the compound $NaHNiD_2$.* This is a yellow-red crystalline substance that is easily decomposed by water and acids. Brown, unstable Li_2NiD_2 was obtained by an analogous procedure. It has now been found that all the oximino-groups of the inner complex palladium dimethylglyoxime also can take part in salt formation. Pure, intensely coloured, stable salts can be obtained, even when working in aqueous solution.

The starting point of the work reported here was the contradictory behaviour of dimethylglyoxime toward ammoniacal palladium solutions as opposed to the action of palladium dimethylglyoxime toward ammonia. Wunder and Thüringer (*Z. anal. Chem.*, 1913, **52**, 101) were the first to describe the quantitative precipitation of palladium dimethylglyoxime from mineral acid solution, and they also pointed out that no precipitate is obtained from ammoniacal solution. The reason for the non-precipitability is that the metal is present not as the reactive Pd^{++} ions but as the stable $[Pd(NH_3)_4]^{++}$ ions. Furthermore, palladium dimethylglyoxime is soluble in ammonia. Since the resulting solution is honey-yellow, it is evident that $[Pd(NH_3)_4]^{++}$ ions are not formed, for they are colourless.

The authors have found that addition of nickel salts to the yellow solution of $Pd(DH)_2$ in ammonia produces no red precipitate, and consequently there can be no unbound dimethylglyoxime present. It was further observed that the yellow solution remained unchanged after acidification with acetic acid followed by addition of potassium iodide. In contrast, this treatment produces insoluble, black palladium iodide, or brown-red solutions of $[PdI_4]^{--}$ ions, when applied to soluble palladium salts or aqueous suspensions of $Pd(DH)_2$. The complete masking of both the dimethylglyoxime and the palladium indicates that the action of ammonia on $Pd(DH)_2$ must produce a compound in which the ratio $Pd : DH_2 = 1 : 2$ has persisted. Consequently, a stable palladium dimethylglyoxime compound in ammoniacal solution can have only a composition which corresponds to that of the ferrous dimethylglyoxime (II) or to the formation of a water-soluble ammonium salt of palladium dimethylglyoxime of the same type as that of the unstable nickel dimethylglyoxime compounds isolated by Thilo and Friedrich. The assumption that an ammonium salt is formed is strengthened by Cooper's finding (*J. Chem. Met. Min. Soc. S. Africa*, 1925, **25**, 296) that $Pd(DH)_2$ dissolves in sodium hydroxide to produce a yellow solution. Confirmation of this supposition is supplied by the fact that compounds can be isolated which by virtue of their composition and chemical behaviour can be regarded as salts of a " dimethylglyoximepalladium acid ". The solubility of $Pd(DH)_2$ in alkalis to form salts, together with the concurrent masking of the palladium and dimethylglyoxime, can thus be plausibly explained by the following stoicheiometric formulations :



or

$$Pd(DH)_2 + 2KOH \longrightarrow K_2[PdD_2] + 2H_2O$$
$$Pd(DH)_2 + 2NH_4OH \longrightarrow (NH_4)_2[PdD_2] + 2H_2O$$

These equations and the isolation of *salts* of a dimethylglyoximepalladium acid represent the conversion of a water-insoluble inner complex salt into a water-soluble compound with an inner complex anion. These changes obviously occur because the two intact oximino-groups that remain in the inner complex palladium dimethylglyoxime form salts with strong alkalis. Accordingly, $Pd(DH)_2$ should be regarded as an amphoteric compound, which functions as an

* The following abbreviations signify: DH_2 = dimethylglyoxime, $C_4H_8O_2N_2$; DH = monobasic residue of dimethylglyoxime, $C_4H_7O_2N_2$; D = dibasic residue of dimethylglyoxime, $C_4H_6O_2N_2$.

inner complex salt in neutral or acid media, and as an acid in alkaline surroundings. Hence, the compounds shortly to be described can be viewed as mixed salts of dimethylglyoxime, in which both oximino-groups exert an acidic function. In view of the fact that Feigl and Rubinstein (*Annalen*, 1923, **433**, 183) isolated cobalt compounds in which dimethylglyoxime is bound solely through the auxiliary valency of the nitrogen of the oximino-groups, it appears that dimethylglyoxime can react in three ways: (1) as neutral portion (DH_2 compounds); (2) as monobasic acid (DH compounds); (3) as dibasic acid (D compounds).

The experimental proof that palladium can form with dimethylglyoxime an inner complex salt as well as an inner complex anion, throws a new light on the ferrous compound of dimethylglyoxime, described by Tschugaeff and Orelkin (*loc. cit.*). There is but little support for the formulation (II) from analogous cases among complex compounds. Rather is it more in keeping with the facts to formulate the compound as an analogue of the water-soluble material produced from $Pd(DH)_2$ and ammonia, *i.e.*, as the ammonium salt of dimethylglyoximeferrous acid, furnishing the red $[FeD_2]^{--}$ ion.

Furthermore, the experimental proof that in the complex-bound dimethylglyoxime the acidic nature of the oximino-groups increases, is in accordance with the following previous findings of one of us (F. F.). The quadrivalent nickel compound $NiO(DH)_2$ (Feigl, *Ber.*, 1924, **57**, 758) and the compound CoS,DH_2,H_2O,NH_3 (Feigl and v. Tustanoswka, *ibid.*, p. 762) are soluble in alkalis and are precipitated from these solutions by addition of acids. Obviously the solubility of these two compounds in alkalis is due to the formation of water-soluble alkali salts.

Experimental.

(1) *Potassium Hydrogen Dimethylglyoximepalladium.*—Highly purified $Pd(DH)_2$ was added in small portions to aqueous potassium hydroxide solution, at 50°, until no more would dissolve. The suspension was filtered warm, and the filtrate, in a closed container, was kept overnight in the refrigerator. Yellow needles deposited and were collected in a glass filtering crucible. Since the salt is readily soluble in water, it was washed free from alkali with absolute alcohol, and the latter was then removed with ether. The material was analysed after 2—4 days' storage in an evacuated desiccator over calcium chloride.

A determination was made of the amount of $Pd(DH)_2$ that remains when the salt is decomposed by means of 0·5N-hydrochloric acid. The acid was allowed to react hot for 30 minutes and then at room temperature overnight. The residue of $Pd(DH)_2$ was collected in a dried, tared filter-paper and washed free from acid with 30% alcohol. After being dried at 105° and weighed, the solid was treated with sulphuric acid, evaporated to dryness, ignited to metallic palladium, and then weighed. The filtrate from the acid treatment was evaporated to dryness, and the residue gently ignited. If the potassium chloride was not perfectly white, the residue was dissolved in water and filtered through a weighed filtering crucible, which was then dried and weighed again. The difference between the weight of the ignited residue and the insoluble material collected on the filter was assumed to represent the weight of the potassium chloride. The analytical data correspond to a *potassium hydrogen* salt with 1·5 mols. of H_2O (after 2 days' drying) and an anhydrous acid salt (after 4 days' drying) (Found, after 2 days' and 4 days' drying, respectively: K, 9·66; 10·75; Pd, 26·80, 29·06; loss on acid treatment, 17·51, 10·91. $KH[PdD_2],1{\cdot}5H_2O$ requires K, 9·73; Pd, 26·54; H_2O, 6·72%. $KH[PdD_2]$ requires K, 10·43; Pd, 28·45%).

(2) *Barium Dimethylglyoximepalladium.*—The *barium* salt must be prepared with scrupulous exclusion of carbon dioxide because the latter readily decomposes the moist product. However, the dry salt is stable against this gas. An aqueous suspension of $Pd(DH)_2$ was boiled to drive off all the carbon dioxide and then allowed to cool. (The container was connected to a guard flask charged with concentrated potassium hydroxide solution.) The suspension was then treated with an excess of freshly prepared, filtered, carbonate-free alcoholic potash. The mixture was shaken until everything went into solution, and then an excess of freshly filtered barium hydroxide solution was added. A yellow, fine-grained precipitate appeared at once. The clear supernatant liquid was siphoned off (with exclusion of carbon dioxide) and the precipitate was washed several times with freshly boiled hot water. When free from alkali, the suspension was filtered through a fine filtering crucible (without exposure to carbon dioxide). The preparation was dried to constant weight in a vacuum over sulphuric acid.

For the analysis, a weighed quantity of the salt was transferred to a tared, fine glass filtering crucible and treated, without applying suction, with 0·5N-hydrochloric acid until the salt was completely decomposed. This point was easily ascertained, both by a change in colour and by an alteration in structure of the solid. The palladium dimethylglyoxime remaining in the crucible was washed thoroughly with water, dried at 105°, and weighed as such. The barium in the filtrate was determined as sulphate. {Found: Ba, 28·58, 28·99; $Pd(DH)_2$, 70·44, 70·55; loss on treatment with acid, 30·00, 29·88. $Ba[PdD_2]$, $0{\cdot}5H_2O$ requires Ba, 28·54; $Pd(DH)_2$, 70·01; H_2O, 1·90%}.

(3) *Palladium Dimethylglyoximepalladium.*—Barium dimethylglyoximepalladium, prepared by the procedure described in (2), was treated with an excess of a neutral solution of palladium chloride (prepared by dissolving ignited palladous chloride in aqueous sodium chloride solution). The mixture was kept on the water-bath, with occasional stirring, until no tiny yellow glistering particles could be seen (about one week). The evaporated water was replaced from time to time. The resulting brown salt was filtered on a glass crucible, the excess of palladous chloride removed by washing with water, and the salt brought to constant weight by drying at 105°. For analysis, the *salt* was decomposed with 0·5N-hydrochloric acid as outlined in (2). Both the residual $Pd(DH)_2$ and the palladium that passed into the filtrate were determined. The latter was precipitated as metallic palladium by making the filtrate basic

with ammonia and then adding formic acid. {Found : Pd, 23·19, 23·54; $Pd(DH)_2$, 72·60, 72·66; loss on treatment with acid, 27·83, 27·79. $Pd[PdD_2],H_2O$ requires Pd, 23·21; $Pd(DH)_2$, 73·30; H_2O, 3·93%.} These data indicate that the compound could be regarded as PdD, *i.e.*, as the palladium salt of dibasic dimethylglyoxime. The synthesis from barium dimethylglyoximepalladium demonstrates, however, that this product is a palladium salt of dimethylglyoximepalladium acid.

(4) *Manganese Dimethylglyoximepalladium.*—This *salt* was prepared as in (3) but by using manganous chloride. The product, dried at 105°, is dark olive green. After decomposition of the salt with 0·5N-hydrochloric acid, the manganese was precipitated as dioxide by treatment of the solution with ammonia and bromine. The dried precipitate was ignited and then converted into manganous sulphate by fuming with sulphurous acid and concentrated sulphuric acid. {Found : Mn, 14·32, 14·52; $Pd(DH)_2$, 85·93, 86·01; loss on treatment with acid, 11·58, 11·54. $Mn[PdD_2]$ requires Mn, 14·09; $Pd(DH)_2$, 86·42%.}

(5) *Lead Salts of Dimethylglyoximepalladium Acid.*—The procedures used in (3) and (4) did not produce pure lead salts of this acid, because $Pb[PdD_2]$ is very sensitive to acids. When barium dimethylglyoxime palladium is treated with an aqueous solution of a lead salt a red precipitate is formed at once. However, this lead salt is not pure; it contains either unreacted $Ba[PdD_2]$ or free $Pd(DH)_2$, depending on the conditions. If palladium dimethylglyoxime is treated with basic acetate ("liquor plumbi subacetici") a red salt is also formed, but this product likewise is not pure. It contains varying proportions of basic lead salts, probably resulting from the hydrolysis of the lead acetate. Nevertheless, by maintaining proper experimental conditions, a neutral and also a basic lead salt of dimethylglyoximepalladium acid were isolated. The products look alike; they are both scarlet when dry. It was found that solutions obtained by dissolving lead hydroxide in aqueous solutions of mannitol, glycerol, etc., react with $Pd(DH)_2$ to form the lead salts. When the mannitol or glycerol solutions are neutral, the normal salt is formed, whereas in the presence of free alkali, the product is a basic salt in which the ratio Pd : Pb = 1 : 2.

(a) *Neutral lead salt.* A solution containing 3·3 g. of lead nitrate in 50 ml. of water was mixed with 50 ml. of glycerol and then with dilute potassium hydroxide solution until the pH was 7·0—7·5. The liquid was then brought to the boil, allowed to cool in a closed container, and after 48 hours was filtered or centrifuged. Palladium dimethylglyoxime was stirred into this solution. The mixture, in a covered beaker, was digested on the water-bath for about 4 hours with occasional stirring. The solid was collected on a glass filtering crucible, washed free from lead with 50% glycerol, and the glycerol was then washed out with water. The solid was brought to constant weight at 105°. The *salt* was analyzed by dissolving the sample in 5—10 ml. of concentrated nitric acid in a beaker. The solution was then cautiously treated with 5 ml. of concentrated sulphuric acid. After the violent reaction had subsided, the mixture was warmed gently, and as soon as no more nitrous gases were evolved the temperature was raised and the solution brought to definite fuming. After cooling, the residue was diluted with 1N-sulphuric acid, to which a little hydrochloric acid had been added in order to dissolve the anhydrous palladium sulphate. The suspension was then heated to boiling, cooled, the lead sulphate collected on a glass filtering crucible, washed, and dried at 120°. The palladium in the filtrate was precipitated by formic acid after the solution had been made alkaline with ammonia (Found : Pb, 38·93, 38·85; Pd, 18·91, 19·21. $Pb[PdD_2]$ requires Pb, 38·22; Pd, 19·68%).

(b) *Basic lead salt.* The *compound* was prepared by the procedure given in (a) except that the addition of potassium hydroxide was continued until the glycerol–lead solution became quite basic to phenolphthalein. {Found : Pb, 51·83, 52·46; Pd, 11·23, 10·50. $Pb[PdD_2],Pb(OH)_2$ requires Pb, 52·90; Pd, 13·62%}.

Attempts to prepare the methyl ester of dimethylglyoximepalladium acid, by refluxing a chloroform solution of methyl iodide along with $Pb[PdD_2]$, were unsuccessful : no yellow lead iodide was formed, nor did evaporation of the chloroform solution yield a noticeable residue.

The authors are indebted to Dr. Ralph E. Oesper, University of Cincinnati, Cincinnati, Ohio, for translating this paper.

LABORATORIO DA PRODUÇÃO MINERAL, MINISTERIO DA AGRICULTURA,
RIO DE JANEIRO, BRAZIL. [*Received, May 17th*, 1947.

NOTES.

Preparation of Some p-*Alkylsulphonylbenzylammonium Chlorides.* By J. CYMERMAN, A. KOEBNER, and W. F. SHORT.

THE *p*-alkylsulphonylbenzylammonium chlorides described in Table I were prepared in 1944—1945 by the following methods :

(A) $p\text{-Cl}\cdot SO_2\cdot C_6H_4\cdot CN \longrightarrow H\cdot SO_2\cdot C_6H_4\cdot CN \longrightarrow R\cdot SO_2\cdot C_6H_4\cdot CN \longrightarrow R\cdot SO_2\cdot C_6H_4\cdot CH_2\cdot NH_2)Cl$

(B) $p\text{-Cl}\cdot SO_2\cdot C_6H_4\cdot CH_2\cdot NHAc \longrightarrow H\cdot SO_2\cdot C_6H_4\cdot CH_2\cdot NHAc \longrightarrow R\cdot SO_2\cdot C_6H_4\cdot CH_2\cdot NHAc$

The reduction of *p*-cyanobenzenesulphonyl chloride to *p*-cyanobenzenesulphinic acid is described by Walker (B.P. 580,884; 26.1.1944), Andrewes, King, and Walker (*Proc. Roy. Soc.*, 1946, *B*, **133**, 51), and Fuller, Tonkin, and Walker (*J.*, 1945, 636), who also alkylated the sulphinic acid and reduced two of the resulting *p*-alkylsulphonylphenyl cyanides to *p*-alkylsulphonylbenzylammonium chlorides. In method

(B), we have improved the yield of *p*-acetamidomethylbenzenesulphonyl chloride (Bergeim and Braker, *J. Amer. Chem. Soc.*, 1944, **66**, 1459). Jensen and Schmith (*Z. physiol. Chem.*, 1944, **280**, 37) describe the reduction of this chloride to *p*-acetamidomethylbenzenesulphinic acid and conversion into *p*-methylsulphonylbenzylammonium chloride but an abstract of this paper was not available until long after we had completed our experiments. The reduction of the sulphonyl chloride has since been described by Dewing (*J.*, 1946, 467) and by Carter and Hey (this vol., p. 147).

TABLE I.

p-*Alkylsulphonylbenzylammonium chlorides.*

p-R·SO$_2$·C$_6$H$_4$·CH$_2$·NH$_3$}Cl; R =	Method.	Yield, %.*	M. p.	Formula.	Found, N, %.	Calc. or reqd., N, %.
(1) Methyl	A and B	*ca.* 100 and 32	275—278°	$C_8H_{12}O_2NClS$	6·4	6·3
(2) Ethyl	A	85	230	$C_9H_{14}O_2NClS$	6·0	5·95
(3) n-*Propyl*	B	—	238—240	$C_{10}H_{16}O_2NClS$	5·6	5·6
(4) iso*Propyl*	A	95	221—222	$C_{10}H_{16}O_2NClS$	5·6	5·6
(5) n-*Butyl*	B	—	267—268	$C_{11}H_{18}O_2NClS$	5·5	5·3
(6) sec.-*Butyl*	A	96	201—202	$C_{11}H_{18}O_2NClS$	5·5	5·3
(7) n-*Amyl*	A	87	265—266	$C_{12}H_{20}O_2NClS$	5·05	5·05
(8) n-*Hexyl*	A	86	263—265	$C_{13}H_{22}O_2NClS$	5·0	4·8
(9) n-*Heptyl*	A	95	260—261	$C_{14}H_{24}O_2NClS$	4·7	4·6
(10) n-*Octyl*	A	90	261·5—262	$C_{15}H_{26}O_2NClS$	4·55	4·4
(11) n-*Hexadecyl*	B	—	235—245	$C_{23}H_{42}O_2NClS$	3·4	3·2
(12) *Benzyl*	B	—	265—270	$C_{14}H_{16}O_2NClS$	4·8	4·7
(13) *Phenyl*	A	45	258—260	$C_{13}H_{14}O_2NClS$	4·9	4·9

* Yields by method (A) are expressed as percentage of theoretical calculated on the cyanide used. In method (B) the yield is calculated on the acetobenzylamide.

(1) Jensen and Schmith (*loc. cit.*) prepared this compound by method (B) and record m. p. 265°. Fuller, Tonkin, and Walker (*loc. cit.*) obtained an 86% yield, m. p. 279—280°, by reduction in 10% ethanolic ammonia at 15—70°/95 atmospheres.

(2) Preparation by Dr. T. D. Robson. The *p*-ethylsulphonylphenyl cyanide was prepared as described by Oxley, Partridge, Robson, and Short (*J.*, 1946, 763). Fuller, Tonkin, and Walker (*loc. cit.*) obtained *p*-ethylsulphonylbenzylammonium chloride, m. p. 222°, in 73% yield, by reduction in saturated ethanolic ammonia at 70 lbs./sq. in.

(13) p-*Cyanodiphenyl sulphone*, m. p. 117—118° (Found: N, 5·8. $C_{13}H_9O_2NS$ requires N, 5·8%), was obtained in 74% yield by heating the corresponding acid (Meyer, *Annalen*, 1923, **433**, 338) and benzenesulphonamide (2 mols.) at 225—230° for 2 hours (cf. Oxley *et al.*, *loc. cit.*).

p-*Cyanobenzenesulphinic Acid.*—A solution of *p*-cyanobenzenesulphonyl chloride (20 g.) (Remsen, Hartman, and Muckenfuss, *Amer. Chem. J.*, 1896, **18**, 156) in hot acetone (30 c.c.) was added during 30 minutes to a well-stirred solution of sodium sulphite heptahydrate (50 g.; 2 mols.) in water (100 c.c.) at 75—80°, the solution being kept alkaline to litmus throughout by periodical addition of sodium carbonate. Heating and stirring were continued for a further 1½ hours, and the sulphinic acid (14 g.; 84·5%), precipitated at 0° by acidification with concentrated hydrochloric acid and collected in ethyl acetate, crystallised from hot water in prismatic plates, m. p. 121—122° (Found: N, 8·55; S, 19·3. Calc. for $C_7H_5O_2NS$: N, 8·4; S, 19·2%). Andrewes, King, and Walker (*loc. cit.*) record m. p. 126—127°, and Fuller, Tonkin, and Walker (*loc. cit.*), m. p. 128—129°. If extraction of the acid solution with ethyl acetate was delayed, a solid separated, and crystallisation from aqueous ethanol gave needles of *bis*-p-*cyanophenyl disulphoxide*, m. p. 158—159° (Found: C, 55·85; H, 2·6; N, 9·45. $C_{14}H_8O_2N_2S_2$ requires C, 56·0; H, 2·7; N, 9·35%).

Alkylation of p-*Cyanobenzenesulphinic Acid.*—A solution of the sodium salt in 50% aqueous ethanol was refluxed with the alkyl halide (1·1—1·2 mols.) for 4—24 hours (see Table II). The *p*-alkylsulphonylphenyl cyanides, precipitated by adding water and crystallised from aqueous alcohol, had the properties recorded in Table II.

Reduction of p-*Alkylsulphonylphenyl Cyanides.**—An approx. 5% solution of the *p*-alkylsulphonylphenyl cyanide in 15% (w/w) methanolic ammonia was shaken with Raney nickel (*ca.* 0·5 g. per g. of cyanide) at 25° in an atmosphere of hydrogen at an initial pressure of 50 lbs./sq. in. When 5 g. of cyanide were used reduction was complete in 1—3 hours. The catalyst was removed by filtration, and the filtrate concentrated to a small volume, saturated with dry hydrogen chloride, and evaporated to dryness. The residue of *p*-alkylsulphonylbenzylammonium chloride was purified by crystallisation from methanol and had the properties recorded in Table I.

p-*Acetamidomethylbenzenesulphonyl Chloride.*—The method of Bergeim and Braker (*loc. cit.*), which gives a 45% yield, was slightly modified. Acetobenzylamide (100 g.) was added during 45 minutes to chlorosulphonic acid (300 c.c.) so that the temperature remained below 15°. The mixture was stirred for an hour at room temperature and then for an hour at 50—60°. The solution was cooled and poured on crushed ice, and the oil which separated solidified when triturated with water containing 2% of ether. After being washed with water and dried in a vacuum the sulphonyl chloride (100 g.; 60%) had m. p. 96—98°. Bergeim and Braker (*loc. cit.*) stated that the pure chloride has m. p. 95—97°.

p-*Acetamidomethylbenzenesulphinic Acid.*†—The preceding sulphonyl chloride (248 g.) and a solution

* See also Boots Pure Drug Co., Koebner, Robson, and Short, B.P. 583,585 (6.10.1944).

† See also Boots Pure Drug Co. Ltd., Koebner and Short, B.P. 584,584 (5.1.1945).

TABLE II.

p-Alkylsulphonylphenyl cyanides from p-*cyanobenzenesulphinic acid.*

p-R·SO_2·C_6H_4·CN; R =	Yield, %.*	Time, hrs.	M. p.	Formula.	Found, N, %.	Calc. or reqd., N, %.
(1) Methyl	80	4	142·5—143·5°	$C_8H_7O_2NS$	—	—
(2) *n*-Propyl	75	6	84—85	$C_{10}H_{11}O_2NS$	6·8	6·7
(3) iso*Propyl*	36	15	102	$C_{10}H_{11}O_2NS$	6·6	6·7
(4) *n*-Butyl	80	20	79—80	$C_{11}H_{13}O_2NS$	6·45	6·3
(5) sec.-*Butyl*	50	18	71—72	$C_{11}H_{13}O_2NS$	6·4	6·3
(6) n-*Amyl*	85	19	90—91	$C_{12}H_{15}O_2NS$	5·95	5·9
(7) n-*Hexyl*	90	18	87—88	$C_{13}H_{17}O_2NS$	5·7	5·6
(8) n-*Heptyl*	85	20	96—97	$C_{14}H_{19}O_2NS$	5·5	5·3
(9) n-*Octyl*	75	20	97—97·5	$C_{15}H_{21}O_2NS$	5·15	5·0
(10) n-*Hexadecyl*	95	24	111·5—112	$C_{23}H_{37}O_2NS$	3·7	3·6
(11) Benzyl	95	21	195·5—196	$C_{14}H_{11}O_2NS$	5·55	5·45

* Overall yield from *p*-cyanobenzenesulphonyl chloride.

(1) Prepared from *p*-methylsulphonylaniline in 65% yield by Walker (*loc. cit.*) and by Fuller, Tonkin, and Walker (*loc. cit.*), who record m. p. 141°. Oxley *et al.* (*loc. cit.*) obtained the cyanide, m. p. 142—143°, in 75% yield from *p*-methylsulphonylbenzoic acid and benzenesulphonamide.

(2) Obtained in 80% yield by reduction of the corresponding allyl compound by Fuller *et al.* (*loc. cit.*), who record m. p. 84—85°, and in 64% yield from *p*-*n*-propylsulphonylbenzoic acid and benzenesulphonamide by Oxley *et al.* (*loc. cit.*) who give m. p. 83—84°.

(4) Prepared from sodium *p*-cyanobenzenesulphinate in 69% yield by Fuller *et al.* (*loc. cit.*) who record m. p. 75—76°.

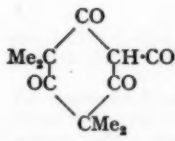
(11) Fuller *et al.* (*loc. cit.*) record m. p. 194—195° for a preparation obtained from the sulphinate in 79% yield.

of sodium sulphite heptahydrate (378 g.; 1 mol.) in water (750 c.c.) were stirred at room temperature, and sodium hydrogen carbonate (170 g.; 2 mols.) was added in portions so that the mixture remained alkaline to litmus throughout. Reduction was complete in 2 hours, and the solution was saturated with sodium chloride to precipitate the rest of the sodium *p*-acetamidomethylbenzenesulphinate. Careful acidification of a solution of this salt at 0° afforded the sulphinic acid, which separated from water in colourless plates, m. p. 139—140° (Found: N, 6·5. Calc. for $C_9H_{11}O_3NS$: N, 6·6%); yield, *ca.* 75%. Jensen and Schmith (*loc. cit.*) record m. p. 137—138°, Dewing (*loc. cit.*) m. p. 148°, and Carter and Hey (*loc. cit.*) m. p. 138°.

p-Alkylsulphonylbenzylammonium Chloride from p-*Acetamidomethylbenzenesulphinic Acid.*—A solution of crude sodium *p*-acetamidomethylbenzenesulphinate in 50% aqueous ethanol was refluxed for 3 hours with the alkyl iodide (1·2 mols.), and the solution was then evaporated almost to dryness in a vacuum. The residue was triturated with cold 5% aqueous sodium thiosulphate, the solid was collected, washed with a little ice-water, and hydrolysed by refluxing for 2 hours with 2·5N-hydrochloric adid. The solution was then concentrated to a small volume, and the crude *p*-alkylsulphonylbenzylammonium chloride was collected and purified by crystallisation from alcohol. The yield of *p*-methylsulphonylbenzylammonium chloride was 71%, but the analogues (Nos. 3, 5, 11 and 12 in Table I) were obtained in small yield.—RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO. LTD., NOTTINGHAM. [*Received, April 10th*, 1947.]

A Synthesis of Leptospermone. By L. H. BRIGGS, C. H. HASSALL, and W. I. TAYLOR.

THE formula shown, suggested by Briggs, Penfold, and Short (*J.*, 1938, 1193) for leptospermone, a constituent of the essential oil of *Leptospermum scoparium*, was recently substantiated by degradative methods (Briggs, Hassall, and Short, *J.*, 1945, 706). Its structure has now been confirmed synthetically by the methylation of phlor*iso*valerophenone.



A solution of phlor*iso*valerophenone (2 g.) (Kenney and Robertson, *J.*, 1939, 1601) in potassium hydroxide solution (2·15 g. in 10 c.c.) and methyl iodide (5·4 g.) were heated electrically in a sealed tube to 70° and shaken for 3 days. After cooling, the heavy brown insoluble layer was dried and distilled at 10 mm., yielding a fraction, 0·788 g., $n_D^{23°}$ 1·492—1·513 (bath temp. 120—140°), soluble in sodium hydroxide solution and giving a red coloration with ferric chloride.

The *p*-toluidino-compound, prepared from 79 mg. according to Briggs, Hassall, and Short (*loc. cit.*), formed pale yellow needles, m. p. 100°, undepressed by pure *p*-toluidinoleptospermone.

The anilino-compound prepared in the same way from 63 mg. crystallised from 60% alcohol in long colourless needles, m. p. 92°, undepressed by anilinoleptospermone.

The *benzylamino*-compound prepared by heating this fraction (78 mg.) with benzylamine (93 mg.) for a few minutes was worked up as for the above compounds. After crystallisation from light petroleum (b. p. 40—50°) and 60% alcohol it formed long rods, m. p. 99°, undepressed by a similar derivative of the same m. p. from natural leptospermone (Found: C, 74·7; H, 8·3. $C_{23}H_{29}O_2N$ requires C, 74·4; H, 8·2%). This derivative exists in polymorphic forms (cf. Chattaway and Lambert, *J.*, 1915, 1766), that from natural leptospermone crystallising in plates from the same solvent as for the synthetic sample, but crystallising in rods of the same m. p. on seeding with this form. However, on seeding a solution of the synthetic material with the plate form only a partial conversion into the plate form could be achieved.

The remainder of the fraction was converted into the benzylamino-compound. This (230 mg.) was

hydrolysed with oxalic acid (200 mg.) in aqueous alcohol for two days at 100°. The regenerated leptospermone separating after removal of the alcohol was purified by distillation in a micro-column [Craig, *Ind. Eng. Chem.* (*Anal.*), 1936, **8**, 219], and then had $n_D^{25°}$ 1·4975, $n_D^{19·5°}$ 1·5007 (Briggs, Penfold, and Short, *loc. cit.*, record $n_D^{19·5°}$ 1·5000 for the natural compound) (Found: C, 67·8; H, 8·5. Calc. for $C_{15}H_{22}O_4$: C, 67·6; H, 8·3%).

We are grateful to the Chemical Society and the Royal Society of New Zealand for grants, and to Mr. R. N. Seelye for the combustion data. One of us (W. I. T.) is indebted for a Duffus Lubecki Scholarship.—AUCKLAND UNIVERSITY COLLEGE, NEW ZEALAND. OTAGO UNIVERSITY, DUNEDIN, NEW ZEALAND. [*Received, April 15th*, 1947.]

The Preparation of o-*Nitroacetophenone.* By K. SCHOFIELD and T. SWAIN.

ALTHOUGH the nitration of acetophenone is a source of pure *m*-nitroacetophenone, the *o*-isomer formed at the same time cannot be freed completely from the *m*-compound (Simpson *et al.*, *J.*, 1945, 646; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 465). The classical acetoacetic ester condensation with *o*-nitrobenzoyl chloride has been effected in two ways: by using sodium ethoxide in absolute alcohol (Needham and Perkin, *J.*, 1904, **85**, 148; McCluskey, *J. Amer. Chem. Soc.*, 1922, **44**, 1573), and by using a suspension of sodioacetoacetic ester in ether (Gevekoht, *Annalen*, 1883, **221**, 323; Ruggli and Reichwein, *Helv. Chim. Acta*, 1937, **20**, 913). Whilst the hydrolysis of the intermediate ethyl *o*-nitrobenzoylacetoacetate, according to Kermack and Smith (*J.*, 1929, 814) gave excellent results, in our hands the first method of effecting the condensation has not proved uniformly satisfactory, since it appears to depend very critically on the quality of the ethanol used. The separation of sodium *o*-nitrobenzoylacetoacetic ester was usually very slow and in several experiments incomplete, and the modification suggested by McCluskey (*loc. cit.*) was unsuitable. Yields of *o*-nitroacetophenone were never higher than 65%, and often much lower. The method is evidently unsatisfactory for large scale work (cf. Ford-Moore and Rydon, *J.*, 1946, 679). In contrast, by using a suspension of the sodio-compound in ether, decomposing the reaction product with dilute acid, and extracting with ether (cf. Ruggli and Reichwein, *loc. cit.*) steady yields of ca. 65% of *o*-nitroacetophenone were obtained, which, though not so high as those claimed by the Swiss authors, were completely reliable. The yield was the same whether the mixture was kept overnight, or refluxed and stirred for 3 hours.

We then decided to investigate the use of malonic ester in this synthesis, but since our work was done two other preparations of *o*-nitroacetophenone have been described. Ford-Moore and Rydon (*loc. cit.*) obtained it from both phenylmethylcarbinol and ethylbenzene, whilst Walker and Hauser (*J. Amer. Chem. Soc.*, 1946, **68**, 1386) utilised the reaction between *o*-nitrobenzoyl chloride and the ethoxymagnesium-derivative of ethyl malonate. Our experiments are complementary to the work of the American authors, and illustrate a possible shortcoming to the use of malonic ester in such reactions, and we describe them briefly. Bischoff and Rach (*Ber.*, 1884, **17**, 2781, 2788) showed that reaction between *o*-nitrobenzoyl chloride (1 mole) and ethyl sodiomalonate (1 mole) yielded ethyl di-(*o*-nitrobenzoyl)-malonate, m. p. 93°, whilst reaction of the acid chloride (1 mole) with ethyl disodiomalonate (1 mole) gave ethyl *o*-nitrobenzoylmalonate, m. p. 54°. We have checked the first statement, and also find that using two equivalents of ethyl sodiomalonate to one of acid chloride gives ethyl *o*-nitrobenzoylmalonate, as proved by hydrolysis to *o*-nitroacetophenone. This is illustrated by the selection of experiments tabulated below, in each of which 0·12 mole of acid chloride was used:

Ethyl sodiomalonate (moles).	Medium.	Conditions.	Yield of *o*-nitroacetophenone (%).
0·26	Benzene	1*a*	73
,,	Ether	,,	70
,,	,,	1*b*	57
,,	,,	1*c*	71
,,	,,	2*b*	79
0·14 *	,,	1*a*	20

(1) At room temperature for 24 hours. (2) Refluxed and stirred for 2 hours, then kept for 12 hours more. (*a*) Hydrolysis by refluxing for 4 hours with 250 c.c. of 35% sulphuric acid. (*b*) Hydrolysis according to Walker and Hauser (*loc. cit.*). (*c*) As (*b*) but prolonged by 5 hours.

* Here the total product of the condensation, a mixture of oil and crystals of the di(nitrobenzoyl) compound, was submitted to hydrolysis. Besides the *o*-nitroacetophenone, 10·7 g. of ethyl di-(*o*-nitrobenzoyl)malonate, m. p. 93°, and 1·5 g. of *o*-nitrobenzoic acid were recovered, suggesting that partial fission of the diacyl compound had occurred.

Clearly, the use of two moles of the monosodium compound, with refluxing and stirring, provides yields of the order claimed by Walker and Hauser (*loc. cit.*); also, the heterogeneous hydrolysis (*a*) would appear to be equally efficient with that in homogeneous solution (*b*). Whether this limitation, necessitating the use of two moles of sodiomalonic ester in such condensations is general has not been investigated, but in the few examples of similar reactions noted in the literature (cf. Wilds and Beck, *J. Amer. Chem. Soc.*, 1944, **66**, 1688; Atkinson and Simpson, *J.*, 1947, 232; Gabriel and Lowenberg, *Ber.*, 1918, **51**, 1493) authors appear to have employed at least a molar excess of the ester. In our opinion, for both convenience and economy, the method of Walker and Hauser (*loc. cit.*) is the best yet described for the preparation of *o*-nitroacetophenone.—UNIVERSITY COLLEGE, EXETER. [*Received, April 21st*, 1947.]

The Interaction of Tetra-arylglycols and Pyridinium Salts. By ALEXANDER SCHÖNBERG and AHMED MUSTAFA.

THE discovery (Schönberg and Michaelis, *J.*, 1936, 1571) that tetraphenylglycol reacts in benzene with pyridine in presence of ethereal hydrogen chloride, forming a crystalline addition product $CPh_2(OH)\cdot CPh_2\cdot OH,C_5H_5N,HCl$, has now been investigated more fully and the reaction found to be of wide application; hydrogen chloride may be replaced by hydrogen bromide; pyridine may be replaced by α-picoline, 2 : 3-lutidine, quinoline, or quinaldine; tetraphenylglycol may be replaced by 9 : 10-dihydroxy-9 : 10-diphenyldihydrophenanthrene or ωωω'ω'-tetraphenyl-*p*-xylylene glycol, $C_6H_4(CPh_2\cdot OH)_2$. Nine new compounds of the above type have been obtained in crystalline form. They are all colourless and can be kept in a closed vessel for months without decomposition; they are destroyed by the action of aqueous alkali, with regeneration of the glycol.

Experimental.—(1) *Complexes from Tetraphenylglycol.* (a) Tetraphenylglycol (0·5 g.) was dissolved in hot benzene (5 c.c.; dried over sodium; thiophen-free), followed by addition of α-picoline (0·3 g.). The mixture was cooled to room temperature, a saturated dry ethereal solution of hydrogen chloride (10 c.c.) added, and the vessel immediately closed and cooled. The ether–benzene layer was then decanted, and the remaining crystals were boiled with absolute ethyl alcohol (6 c.c.) and collected; this residue (0·6 g.) was immediately recrystallised from absolute ethyl alcohol, forming crystals, m. p. *ca.* 190° (decomp., efferv., red melt) (Found: C, 77·4; H, 6·2; N, 2·8; Cl, 7·5. $C_{32}H_{30}O_2NCl$ requires C, 77·5; H, 6·1; N, 2·8; Cl, 7·2%). The addition *product* is very difficultly soluble in cold water.

(b) 2 : 3-Lutidine similarly gave crystals from absolute ethyl alcohol, m. p. *ca.* 190° (decomp., red-brown melt) (Found: C, 77·4; H, 6·3; N, 2·9; Cl, 7·3. $C_{33}H_{32}O_2NCl$ requires C, 77·7; H, 6·3; N, 2·7; Cl, 7·0%).

(c) The *product* from quinoline, crystallised from benzene–absolute ethyl alcohol, had m. p. *ca.* 198° (decomp., red-brown melt); it was difficultly soluble in hot absolute ethyl alcohol (Found: C, 78·6; H, 5·8; N, 2·5; Cl, 7·0. $C_{35}H_{30}O_2NCl$ requires C, 79·0; H, 5·7; N, 2·6; Cl, 6·7%).

(d) An additive *compound* from pyridine was obtained as in (a), but with use of dry, ethereal hydrogen bromide; it crystallised from absolute ethyl alcohol; m. p. *ca.* 195° (decomp.) (Found: N, 2·4; Br, 15·3. $C_{31}H_{28}O_2NBr$ requires N, 2·7; Br, 15·2%).

(2) *Complexes from* 9 : 10-*dihydroxy*-9 : 10-*diphenyldihydrophenanthrene.* (a) This glycol (1 mol.) (Werner and Grob, *Ber.*, 1904, **37**, 2902) and pyridine (2½ mols.) were allowed to react in the presence of dry ethereal hydrogen chloride, as described above. The *complex* formed crystals from hot absolute ethyl alcohol, m. p. *ca.* 238—239° (decomp.) (Found: C, 77·3; H, 6·0; N, 2·8; Cl, 6·8. $C_{31}H_{28}O_2NCl$ requires C, 77·6; H, 5·5; N, 2·9; Cl, 7·4%). When treated with aqueous alkali on the boiling water-bath, they evolved pyridine and regenerated 9 : 10-dihydroxy-9 : 10-diphenyldihydrophenanthrene (m. p. and mixed m. p.).

(b) From α-picoline similarly were obtained crystals, m. p. *ca.* 200° (decomp.), from absolute ethyl alcohol (Found: C, 77·1; H, 6·3; N, 2·5; Cl, 7·5. $C_{32}H_{28}O_2NCl$ requires C, 77·8; H, 5·7; N, 2·9; Cl, 7·2%).

(3) *Complexes from* ωωω'ω'-*tetraphenyl*-p-*xylylene glycol.* The glycol (1 mol.) (Ullmann and Schlaepfer, *Ber.*, 1904, **37**, 2003) and pyridine were treated as described above. An additive *product* was obtained from absolute ethyl alcohol, m. p. *ca.* 215° (decomp., red-brown melt) (Found: C, 79·8; H, 6·2; N, 2·1; Cl, 6·1. $C_{37}H_{32}O_2NCl$ requires C, 79·6; H, 5·8; N, 2·5; Cl, 6·4%). The *product* from quinoline, crystallised from absolute ethyl alcohol, had m. p. *ca.* 240° (with decomposition and red brown melt) (Found: C, 80·8; H, 5·3; N, 2·7; Cl, 5·8. $C_{41}H_{34}O_2NCl$ requires C, 81·0; H, 5·6; N, 2·3; Cl, 5·8%); and that from quinaldine, similarly crystallised, had m. p. *ca.* 235° (decomp., brown melt) (Found: C, 80·8; H, 5·8; N, 2·6; Cl, 5·8. $C_{42}H_{34}O_2NCl$ requires C, 81·1; H, 5·8; N, 2·3; Cl, 5·7%).—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, ABBASSIA-CAIRO, EGYPT. [*Received, May 1st*, 1947.]

Recent Developments in the Vitamin A Field.

THE PEDLER LECTURE DELIVERED ON DECEMBER 4TH, 1947.

By SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S.

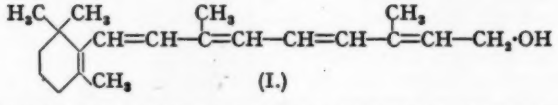
ALTHOUGH the primary object of this lecture is to place before you some of the recent developments in the chemistry of vitamin A which have led to the ultimate goal of synthesis, in order that my narrative may be complete I would like briefly to recall some of the more salient points in its early chapters.

It is difficult precisely to state the actual year in which the vitamin was recognised as a specific substance, but the discovery is generally ascribed to McCallum and Davis who found that whereas growth ceased prematurely with young rats fed on synthetic diets in which fat was supplied as lard, it was immediately resumed if either butter fat or an ether extract of egg yolk was added to the diet (*J. Biol. Chem.*, **1913**, **15**, 167; cf. also Osborne and Mendel, *ibid.*, p. 311). In 1922, clear evidence was adduced that animal fats and fish-liver oils contain two distinct vitamins, the one now known as vitamin A, which was found to be directly associated with growth, antixerophthalmic activity, and night blindness, and the other, vitamin D, the antirachitic factor (McCallum *et al.*, *ibid.*, 1922, **53**, 293). The next few years saw attention mainly directed to the working out of satisfactory methods of the detection and estimation of the vitamin.

First and foremost came, of course, the biological assay, the final arbiter of physiological potency. This process is unsatisfactory for routine assay purposes, being both time-consuming and laborious; it has now been largely superseded by physical methods. Vitamin A concentrates give a blue colouration with chloroformic antimony trichloride (Carr and Price, *Biochem. J.*, 1926, **20**, 497) the intensity of which depends on the vitamin A content. This may be estimated either colorimetrically by comparison with a standard vitamin A concentrate, or more specifically in terms of the intensity of light absorption at the exhibited maximum, 620 mμ (Gillam and Morton, *ibid.*, 1931, **25**, 1346). The most reliable method of vitamin essay is based on the observation of Morton and Heilbron (*ibid.*, 1928, **22**, 987) that vitamin A exhibits characteristic maximal absorption at 328 mμ, the intensity of light absorption at this point giving a direct measure of the vitamin A content, generally expressed in terms of the extinction coefficient, $E^{1\%}_{1\,cm.}$. An excellent critical survey of the methods of assay of vitamin A and of the need for a satisfactory standardisation of the " International Unit " has been recently made by Gridgeman (*Chem. and Ind.*, 1947, **38**, 574).

The discovery by Poulson in 1929 (*Strahlentherapie*, 1929, **34**, 648) that halibut-liver oil constituted a rich source of the vitamin pointed the way to its isolation in the pure state. Viscous golden-yellow concentrates of up to 70% purity were obtained from the crude oil by application of the methods of chromatography and of molecular distillation (Karrer, Morf, and Schopp, *Helv. Chim. Acta*, 1931, **14**, 1036, 1431; Heilbron, Heslop, Morton, Webster, Rea, and Drummond, *Biochem. J.*, 1932, **26**, 1178). It was not until 1942, however, that Baxter and Robeson succeeded in obtaining pure vitamin A in the form of pale yellow prisms, m. p. 63—64° (*J. Amer. Chem. Soc.*, 1942, **64**, 2411).

Although the isolation of the crystalline vitamin is of such a recent date, its constitution as the polyene alcohol (I) was established as early as 1931 by oxidative degradation experiments (Karrer, Morf, and Schopp, *loc. cit.*). Confirmatory evidence was provided by Heilbron, Morton, and Webster (*Biochem. J.*, 1932, **26**, 1194) who dehydrogenated vitamin A with selenium and isolated 1 : 6-dimethylnaphthalene, thus determining the relative positions of the *gem*-dimethyl group and the first side-chain methyl group. Synthetic evidence for the postulated carbon skeleton was provided by Karrer and Morf (*Helv. Chim. Acta*, 1933, **16**, 625) who established the identity of perhydrovitamin A, the fully hydrogenated compound, with a compound synthesised from β-ionone.



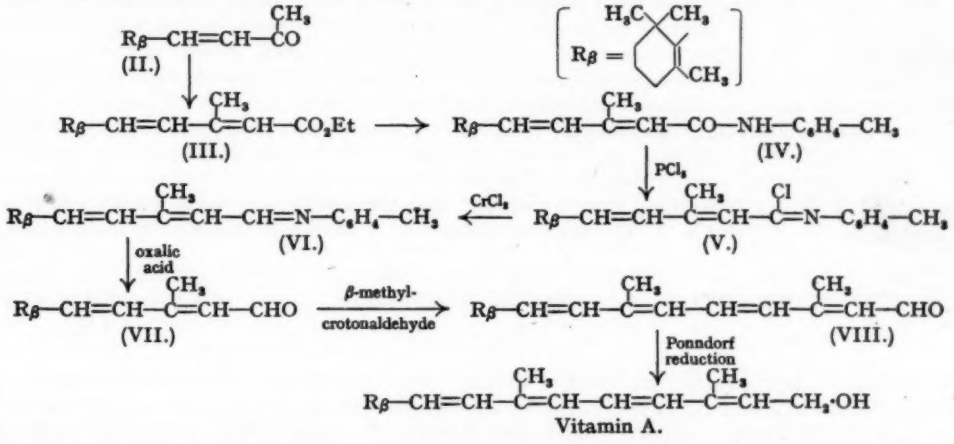
(I.)

Following upon the elucidation of the structure of vitamin A, its synthesis provided the next objective, and this problem has been actively pursued throughout the past decade by workers in many countries.

The most obvious starting point is β-ionone (II), but unfortunately, apart from its normal

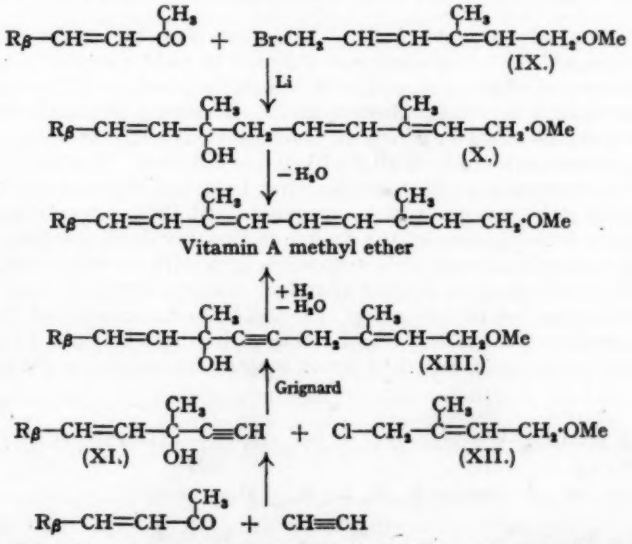
Reformatsky reaction, this ketone behaves anomalously in many ways, notably in condensations involving Grignard reagents (cf. Jones, *Ann. Reports*, 1941, **38**, 180), and this immediately imposes a severe restriction on its potential usefulness.

The first reported synthesis of material showing growth-promoting activity is that of Kuhn and Morris (*Ber.*, 1937, **70**, 853). These workers subjected β-ionone to the usual Reformatsky reaction using ethyl bromoacetate, and obtained ethyl β-ionylideneacetate (III). This was



converted into its *o*-toluidide (IV) and thence into the chloro-imide (V) by phosphorus pentachloride in ether. Reduction of (V) with chromous chloride yielded the *o*-tolil of β-ionylideneacetaldehyde (VI) from which the free aldehyde (VII) was obtained by hydrolysis with oxalic acid. β-Ionylideneacetaldehyde was found to condense with β-methylcrotonaldehyde in the presence of piperidine acetate to yield a product (VIII) which on reduction with aluminium *iso*propoxide furnished a mixture of alcohols which, after partial purification by adsorption on alumina, showed on bioassay a vitamin A content of approximately 5%. Unfortunately, this synthesis has not been found to be reproducible by other workers (Karrer and Ruegger, *Helv. Chim. Acta*, 1940, **23**, 284; Krauze and Slobodin, *J. Gen. Chem. Russia*, 1940, **10**, 907).

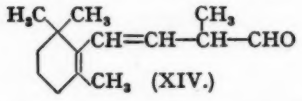
In 1939 Kipping and Wild claimed to have synthesised vitamin A methyl ether by condensing β-ionone with the bromo-ether (IX), using lithium instead of magnesium (*Chem. and Ind.*, 1939,

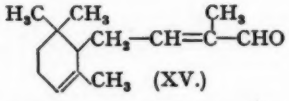


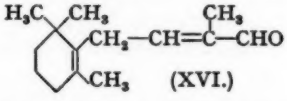
58, 802), but this claim has not been substantiated. Still more recently Oroshnik (*J. Amer. Chem. Soc.*, 1945, **67**, 1627) has published a preliminary note describing the synthesis of vitamin

A methyl ether by the condensation of the ethynylcarbinol (XI) derived from β-ionone with 1-chloro-4-methoxy-2-methylbut-2-ene (XII) followed by semihydrogenation and dehydration. The position of the absorption maximum of the final product, however, is at 3150 A. instead of at 3250 A. as would be expected. This would appear to be due, at least in part, to the presence of a compound containing only four conjugated double bonds. In a private communication, however, Dr. Oroshnik informs me that his product possesses biological activity.

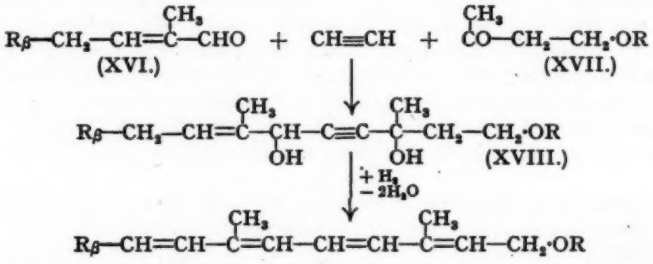
The unsatisfactory and restricted nature of the direct route from β-ionone led us in 1939 to search for more fruitful starting materials. My attention was drawn by my former research assistant, W. E. Jones, to a paper by Ishikawa and Matsuura (*Chem. Zentr.*, 1937, II, 3452) in which what was said to be β-ionone was subjected to a Darzens reaction with ethyl chloroacetate, and the glycide ester so obtained saponified and decarboxylated to give the aldehyde (XIV). We have shown that in fact the aldehyde obtained by these authors must have been the α-ionone derivative (XV) which, as such, is obviously useless for further relevant synthetic work. A complete reinvestigation of the reaction was then carried out using carefully purified β-ionone regenerated from its crystalline semicarbazone, and we finally succeeded in obtaining the αβ-unsaturated C_{14}-aldehyde (XVI), which in contrast to β-ionone reacts normally with Grignard


(XIV.)

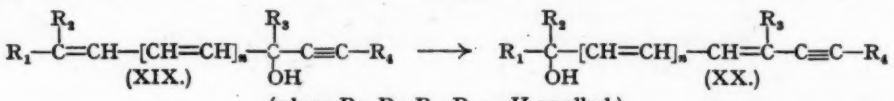

(XV.)

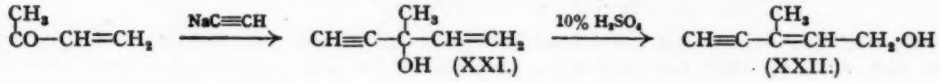

(XVI.)

type reagents. In particular we showed that it condensed readily with sodium acetylide in liquid ammonia and with other acetylenes by the Grignard method to give the normal carbinols (*e.g.*, XXVI) (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727; Cymerman, Heilbron, Jones, and Lacey, *J.*, 1946, 500). The success of this reaction led us to adumbrate the following basic scheme for the synthesis of vitamin A:



The three components—the C_{14}-aldehyde (XVI), acetylene, and a ketobutanol derivative (XVII)—should be capable of being condensed together to yield a product (XVIII), containing the full carbon skeleton of vitamin A, which on semihydrogenation and dehydration would be expected to furnish vitamin A or a simple derivative. There are obviously many permutations and combinations of the methods by which the condensations might be achieved, and it was our intention to make a systematic study of all the likely possibilities. The impact of war, however, severely curtailed our normal research activities after 1940, and we were further hampered by a difficulty in obtaining pure β-ionone which continued until 1946. Accordingly, we decided to embark on a detailed investigation of the main reaction involved, namely, the study of the condensation of αβ-unsaturated carbonyl compounds both with acetylene and with substituted ethynyl derivatives of all types, a subject that had hitherto received scant attention in the literature. This work has led us into many rich and hitherto unexplored pastures of organic chemistry, and a number of novel and useful reactions has been brought to light. One of the most striking of these is the rearrangement which may be formulated in the following manner:

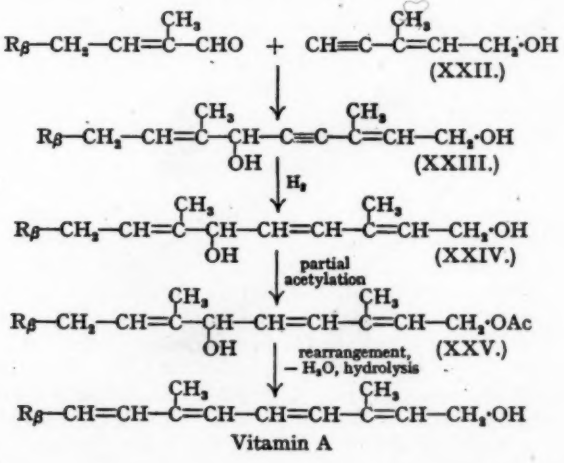

(where R_1, R_2, R_3, R_4 = H or alkyl.)



Structure (XIX) represents the general formulation for an acetylenic carbinol derived from a conjugated polyene carbonyl compound. We have demonstrated that when these compounds are treated with acids a smooth anionotropic rearrangement takes place and the polyene system moves into conjugation with the triple bond to yield fully conjugated compounds of the type (XX) in almost quantitative yields (Jones and McCombie, *J.*, 1943, 261; Heilbron, Jones, *et al.*, *J.*, 1943, 264, 265, 268; 1944, 134, 136, 140, 141, 144; 1945, 27, 77, 90; 1946, 500, 937). We also successfully accomplished the semihydrogenation of the unrearranged acetylenic carbinols of type (XIX) and found that the corresponding ethylenic carbinols rearrange even more easily to yield the fully conjugated polyene carbinols (Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84). It was also found that, if the rearrangement be conducted in a solution of an alcohol, the corresponding rearranged ether is obtained (Heilbron, Jones, and Weedon, *J.*, 1945, 81; Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 88).

Among the compounds we subjected to this reaction was methyl vinyl ketone. This was condensed in normal fashion with sodium acetylide to yield the ethynyl carbinol (XXI) which smoothly isomerised with dilute sulphuric acid to the primary alcohol, 3-methylpent-2-en-4-yn-1-ol (XXII) (Cymerman, Heilbron, and Jones, *J.*, 1945, 90). This compound is obviously a key intermediate in the synthesis of vitamin A as condensation with the C_{14}-aldehyde (XVI) should yield directly a compound containing the full carbon skeleton of vitamin A (Cymerman, Heilbron, Johnson, and Jones, *J.*, 1944, 141). As, however, no C_{14}-aldehyde was then available, we regretfully had to relegate the project to some post-war date and continue with our fundamental, though less spectacular, pioneer work.

Meantime, Isler and his collaborators in Switzerland working in the Hoffman–La Roche laboratories have recently announced the successful synthesis of vitamin A on the above lines, thus confirming the validity of our proposals (*Helv. Chim. Acta*, 1947, **30**, 1911).



The method employed by these authors was to condense the C_{14}-aldehyde with methylpentenynol (XXII) in the normal Grignard manner to obtain the acetylenic carbinol (XXIII), semihydrogenation of which employing a partly poisoned palladium catalyst yielded the polyene glycol (XXIV). The primary hydroxyl group was protected by selective acetylation, and the resulting ester (XXV) treated with a solution of iodine in light petroleum, whereby rearrangement accompanied by simultaneous dehydration occurred giving crude vitamin A acetate. Hydrolysis and purification of the product *via* the anthraquinonecarboxylate yielded crystalline vitamin A identical in every respect with the natural product.

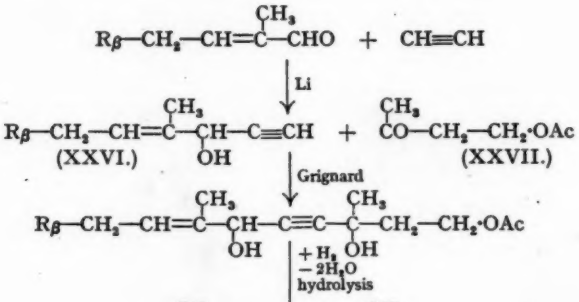
In the same way, using the methyl ester of (XXII), vitamin A methyl ether was obtained; this was found to be nearly as biologically active as the alcohol itself (Isler, Huber, Ronco, and Kofler, *Experientia*, 1946, **2**, 31; Emil Barell Jubilee Volume, Hoffmann-La Roche and Co., Basle, 1946, p. 31).

It should be pointed out that the large-scale production of the synthetic vitamin by this process has only been made possible by the discovery by Isler and his colleagues that the intermediate glycide ester is extremely sensitive to heat and that, therefore, its saponification to the acid must be carried out at about 5°. It was further observed by these workers that under

these precise conditions the acid immediately loses carbon dioxide giving the aldehyde, which, after distillation, is obtained pure in 80% yield, as against the 10—20% previously recorded.

As so often happens, Milas in America seems to have hit on the idea of using the C_{14}-aldehyde for the synthesis of vitamin A about the same time as we did, and in a number of patents has recorded the preparation of materials containing some vitamin A both by a method similar to that adopted by the Swiss workers, and alternatively by condensation of the ethynyl carbinol (XXVI) with ketobutanol acetate (XXVII) followed by the obvious procedures of semihydrogenation, dehydration, and saponification. As this author's work has, apart from a short note, so far only been recorded in a series of patents (U.S.PP. 3,369,156—157; 3,369,166—168; 2,382,085—086; *Science*, 1946, **103**, 581) there is a lack of precise information which is unfortunate, as it renders the work difficult to assess, especially as the C_{14}-aldehyde is regarded as having the $\beta\gamma$-structure (XIV).

I wish now to devote a few minutes to the consideration of still another novel approach to synthetic vitamin A. By the use of *N*-bromosuccinimide (Ziegler *et al.*, *Annalen*, 1942, **551**, 80), methyl γ-bromocrotonate has become readily available, and its use in the Reformatsky reaction when applied to β-ionone has had fruitful results. This reaction has been studied



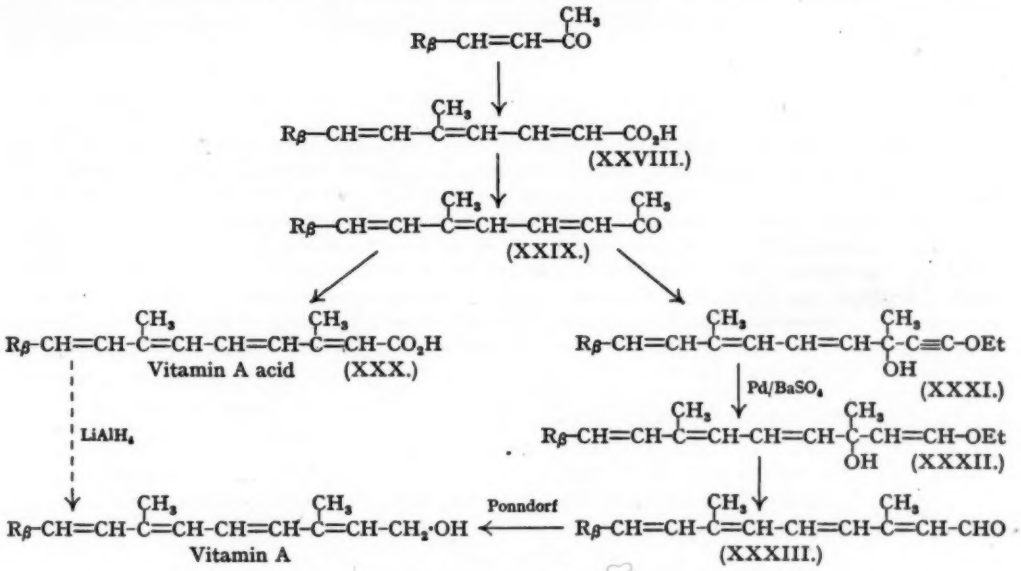
Vitimin A.

contemporaneously by Arens and Van Dorp in Holland (*Rec. Trav. chim.*, 1946, **65**, 338), by Karrer in Switzerland (Karrer, Jucker, and Schick, *Helv. Chim. Acta*, 1946, **29**, 704), and in my own laboratory (Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866), and leads to the crystalline C_{17}-acid (XXVIII). Attempts both on our part and by Karrer and Schwyzer (*Helv. Chim. Acta*, 1946, **29**, 1191) to prepare the corresponding polyene C_{19}-acid with five conjugated ethenoid linkages which we anticipated might have biological activity, by condensing methyl ω-bromosorbate with β-ionone, have been entirely abortive. The next stage, the conversion of the C_{17}-acid to the C_{18}-ketone (XXIX) was handled somewhat differently by each group of workers. In my laboratory the C_{17}-acid chloride was prepared and brought into reaction with dimethylcadmium; Karrer also proceeded *via* the acid chloride, employing zincmethyl iodide as the reactant. The Dutch workers, however, using methyl-lithium (cf. Gilman and van Ess, *J. Amer. Chem. Soc.*, 1933, **55**, 1258), have proceeded directly from the C_{17}-acid to the C_{18}-ketone which they then condensed with ethyl bromoacetate. Hydrolysis of the resultant C_{20}-ester gave " vitamin A acid " in the form of yellow crystals exhibiting maximal absorption at 3470 A. The importance of this synthesis springs from the observation that the sodium salt of the C_{20}-acid, buffered to pH 10, is as biologically active as vitamin A itself. It is also obvious that the application to it of the elegant, recently discovered reagent, lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197), should yield vitamin A directly (cf. Milas and Harrington, *ibid.*, p. 2247).

Arens and van Dorp have further utilised the C_{18} ketone (XXIX) in an elegant synthesis of vitamin A itself (*Nature*, 1947, **160**, 189). They condensed it with ethoxyacetylene (Jacobs, Cramer, and Hanson, *J. Amer. Chem. Soc.*, 1942, **64**, 223) to obtain the acetylenic carbinol (XXXI) which on semihydrogenation yielded the enol ether (XXXII). Anionotropic rearrangement of this compound under the influence of dilute hydrochloric acid furnished vitamin A aldehyde (XXXIII) which, on reduction by the Ponndorf method, furnished an oil containing about 35% of vitamin A.

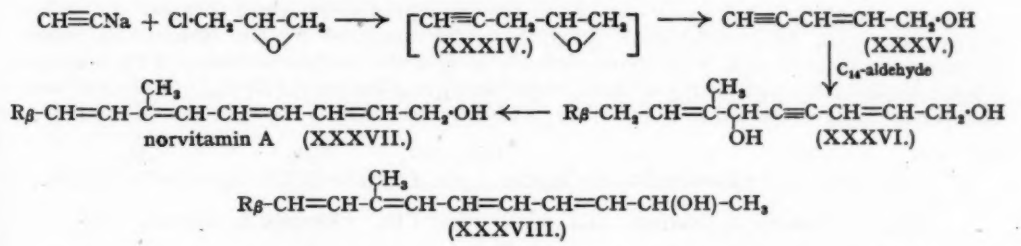
At Imperial College we have now embarked on a comprehensive research programme aimed

at producing modified vitamin A structures. Our general method consists in introducing methyl groups one by one into a basic vitamin A structure completely devoid of all such groups. The



study of the biological activity of these homologous compounds should give a final picture of the mode of dependency of physiological activity on the detailed structure, while at the same time the light absorption exhibited by these compounds should be of considerable interest. I will now give a brief account of some of the reactions we are employing to attain this objective.

The very interesting and useful acetylenic carbinol, pent-2-en-4-yn-1-ol (XXXV), first prepared in my laboratory by a rather lengthy process (Heilbron, Jones, Lacey, McCombie, and Raphael, *J.*, 1945, 77), is now readily available as a result of our observation that it is, rather unexpectedly, the product of the interaction of sodium acetylide and epichlorohydrin in liquid ammonia (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583). This carbinol has now been condensed with the C_{14}-aldehyde (XVI) to give the glycol (XXXVI) from which norvitamin A (XXXVII) has been prepared as a 25% concentrate which exhibits biological activity. A similar condensation has been carried out with the homologous compound hex-3-en-5-yn-2-ol (Jones and McCombie, *J.*, 1943, 261) with the purpose of obtaining (XXXVIII), a modified vitamin A containing a secondary hydroxyl group.

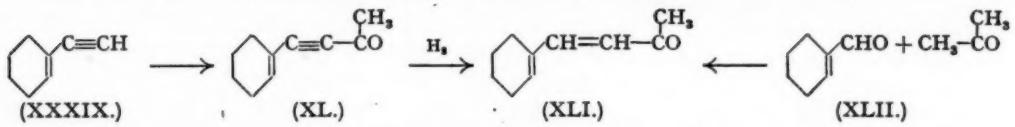


Rβ–CH=CH–C(CH3)=CH–CH=CH–CH=CH–CH=CH–CH(OH)–CH3
(XXXVIII.)

Obvious key intermediates for our project are the various demethyl-β-ionones, and various methods have been worked out for their preparation. I will illustrate some of these routes using as the example the completely demethylated β-ionone (XLI.).

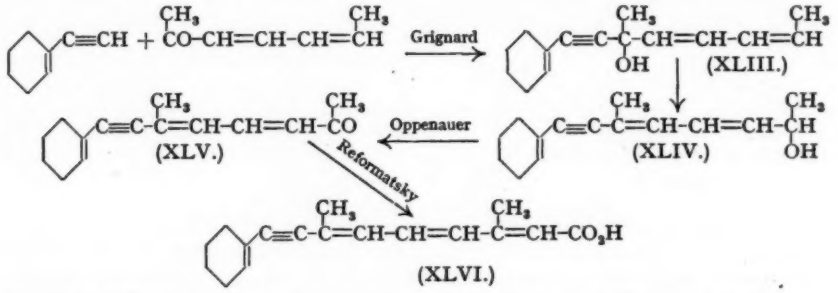
The hitherto ill-defined compound, ethynyl*cyclo*hexene (XXXIX), is now available in quantity as a result of our observation that the acetylene carbinol of *cyclo*hexanone can be dehydrated smoothly over aluminium phosphate. The Grignard complex of this hydrocarbon has been treated with acetic anhydride to furnish the ketone (XL), semihydrogenation of which yielded (XLI). An alternative direct synthesis of (XLI) based on the condensation of *cyclo*-hexenealdehyde (XLII), which has also been made readily available, with acetone has also been

achieved. The resulting demethyl-β-ionone and its homologues are being subjected to reactions similar to those already discussed to furnish the corresponding demethylvitamins.



(XXXIX.) (XL.) (XLI.) (XLII.)

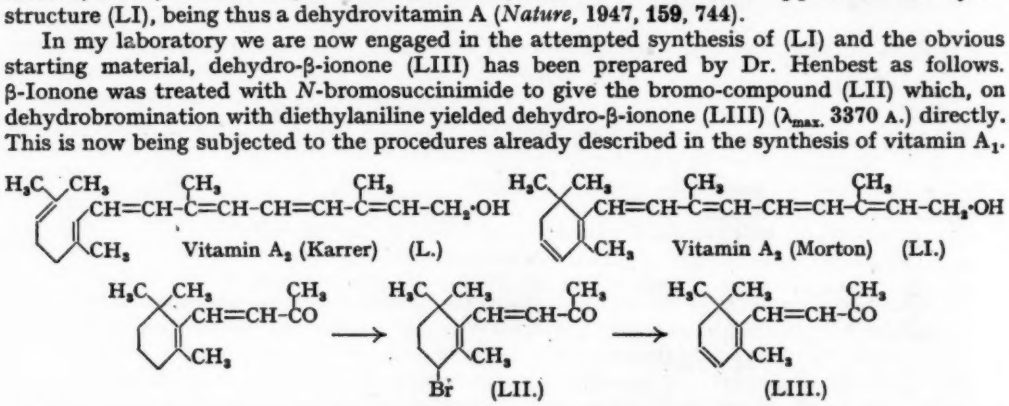
Ethynyl*cyclo*hexene is also the starting material for a synthesis providing a new general method of obtaining lower homologues of vitamin A acid and hence of vitamin A itself. We have condensed the hydrocarbon with the easily obtainable crotonylideneacetone to furnish the carbinol (XLIII) which smoothly undergoes anionotropic rearrangement to the isomeric secondary carbinol (XLIV), which, when oxidised by the Oppenauer method, yields the ketone (XLV). Treatment of this ketone with methyl bromoacetate under Reformatsky conditions readily leads to the crystalline C_{17}-acid (XLVI), analogous to vitamin A acid. This is of considerable interest as it exhibits definite although weak physiological activity. The partial hydrogenation of this acid to produce the modified vitamin A acid itself is now being studied.



(XLVI.)

The accomplishment of the synthesis of vitamin A, or A_1 as it should strictly be designated, has brought into sharp focus the question of the constitution of vitamin A_2, the vitamin associated with fresh-water fish (Gillam, Heilbron, Jones, and Lederer, *Biochem. J.*, 1938, **32**, 405). The structure of this compound has not so far been definitely settled. Karrer and his co-workers, mainly on the basis of the production of acetone on ozonolysis and the absorption maximum at 3450 A., have put forward the open chain formula (L) (*Helv. Chim. Acta*, 1941, **24**, 161E; 1942, **25**, 1650; 1943, **26**, 1758). This formulation, however, fails to explain a large number of facts, among which may be mentioned the circumstance that lycopene, unlike β-carotene, fails to function as a provitamin A_2 (Morton and Creed, *Biochem. J.*, 1939, **33**, 318). Morton, Salah, and Stubbs, on the other hand, consider that vitamin A_2 possesses the cyclic structure (LI), being thus a dehydrovitamin A (*Nature*, 1947, **159**, 744).

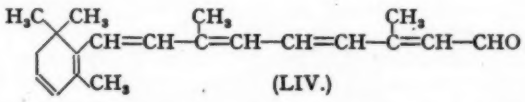
In my laboratory we are now engaged in the attempted synthesis of (LI) and the obvious starting material, dehydro-β-ionone (LIII) has been prepared by Dr. Henbest as follows. β-Ionone was treated with *N*-bromosuccinimide to give the bromo-compound (LII) which, on dehydrobromination with diethylaniline yielded dehydro-β-ionone (LIII) ($\lambda_{max.}$ 3370 A.) directly. This is now being subjected to the procedures already described in the synthesis of vitamin A_1.



A relatively minor symptom of vitamin A deficiency is night blindness, and the fundamental relationship connecting the metabolism of vitamin A and related carotenoids with the biochemical processes in the retinal rods and cones has been the subject of intensive research. One essential stage in the processes of dark-adaptation in the eyes of vertebrates is the

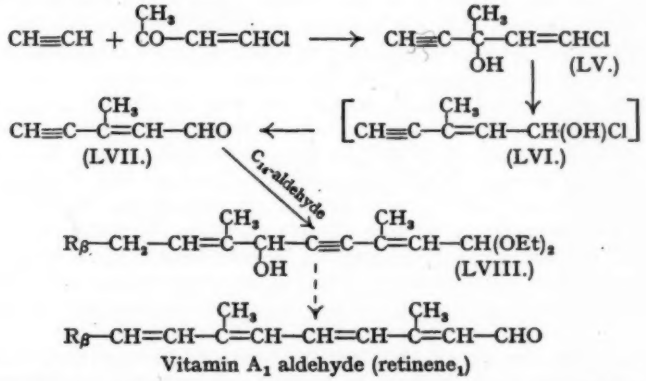
breakdown and regeneration of visual purple in the retinal rods. The visual purple complex obtained from these vertebrates utilising vitamin A_1 in the metabolic processes is a protein termed rhodopsin, the prosthetic group of which, originally believed to be a carotenoid, retinene, has recently been shown to be identical with vitamin A_1 aldehyde (Morton *et al.*, *Nature*, 1944, **153**, 69, 405).

Similarly, the visual purple from vertebrates utilising vitamin A_2 is a closely related protein, porphyropsin, the prosthetic group of which, retinene$_2$, has been shown to be identical with vitamin A_2 aldehyde, which is believed to be (LIV) (Morton, Salah, and Stubbs, *Nature*, 1947, **159**, 744) previously obtained in my laboratory by oxidation of vitamin A_1 with aluminium *tert.*-butoxide in the presence of diethyl ketone (Haworth, Heilbron, Jones, Morrison, and Polya, *J.*, 1939, 128).



(LIV.)

We are also working on the synthesis of vitamin A_1 aldehyde by a new and interesting route. The vital intermediate is the highly reactive aldehyde (LVII), recently prepared by the following method (Jones and Weedon, *J.*, 1946, 938). Methyl chlorovinyl ketone was condensed with sodium acetylide to give the chlorocarbinol (LV), which in the presence of dilute acids rearranged to give (LVII) directly, *via* the hypothetical intermediate (LVI). The diethylacetal of this has been prepared, and by condensation with C_{14}-aldehyde followed by the procedure already described it should yield vitamin A_1 aldehyde.



Vitamin A_1 aldehyde (retinene$_1$)

And so, after many years, victory has come, and the romance of exploration, of high hopes and bitter disappointment, will in a few years simply be recorded in the text-books of organic chemistry in a few terse sentences. Looking back, I still can recapture the excitement of the early days of investigation with Morton and W. E. Jones in Liverpool, with Gillam in Manchester, and with E. R. H. Jones in London. To each of these and to a host of loyal and enthusiastic research students, especially Dr. Raphael and Mr. Sondheimer, I owe a debt of gratitude for their generous help and co-operation.

OBITUARY NOTICES.

VICTOR LEFEBURE.

1891—1947.

VICTOR LEFEBURE was born on September 13th, 1891, at Tufnell Park. He was educated at the William Ellis School, from which he proceeded in 1909 to University College, London, where he obtained the degree of B.Sc. in 1911. He remained at University College until 1914. He was awarded an 1851 Exhibition Scholarship for research and a Tufnel Research Scholarship that year. During this period he was the joint author of chemical papers with Ramsay and Caspari. He then became a lecturer at Wye Agricultural College. During his College days he distinguished himself in both cricket and football. He was also a notable tennis player.

In March 1915 he was commissioned in the 3rd Essex Regiment, from which he was subsequently transferred to the Special Brigade, R.E., constituted in 1915 to undertake offensive operations with the new methods of chemical warfare. As a Company Commander in the Special Brigade he carried out on the night of October 5—6th, 1916, one of the most successful cylinder gas attacks of the war on the French front at Nieuport. Brigadier-General Foulkes, the Commander of the Special Brigade, wrote :

> " Although he was the junior of the two Company Commanders, I put Captain Lefebure in charge of the operation, because he was the better linguist and it was essential that no misunderstandings should occur in making the arrangements with the French Staff."

General Balfourier, the Commander of the French 36th Army Corps in the Nieuport area, paid tribute to the technical skill and success with which the operation was conducted, in spite of intensive German artillery retaliation as soon as the gas discharge started.

In 1917, because of his excellent field knowledge of chemical warfare and his linguistic ability, Lefebure was appointed with the rank of Major as the British Chemical Warfare Liaison Officer with the French, with Headquarters in Paris, and held this appointment until the office was closed in the spring of 1919. In this connection he was a member of the Inter-Allied Secretariat for Chemical Warfare and of the Chemical and Explosives Committees of the Inter-Allied Munitions Council. He carried out his duties in Paris with conspicuous success and was instrumental in putting the relationships between the British and French Chemical Warfare Research and Experimental Departments on an entirely new footing of the closest friendship and collaboration. For his war services he was appointed an officer of the British Empire Order, a Chevalier of the Legion of Honour, and an Officer of the Crown of Italy.

After demobilisation, he joined the British Dyestuffs Corporation Limited at Blackley in April 1919 to take charge of the newly formed development department. He remained there till January 1924, and during the whole of the time did extremely useful work on various products, mainly organic rubber accelerators. He afterwards joined his friend Colonel Mulliner in a small firm making rubber products in Fulham. He was later closely associated with William Willett Limited as Managing Director of one of its subsidiaries. During this period he developed among other things rigid rubber paving blocks and floor tiles with a basis of " Poilite ". He did pioneering work on decorative processes in relation to asbestos and also specialised in, and originated, new types of material for interior decoration made from plastic substances.

Through his association with Mulliner, he became a Director of the Warren Portland Cement Works at Hartlepool where he discovered an anhydrite (calcium sulphate) mine under the cement works. He worked out numerous applications of this material such as quick-setting plasters, and developed its use in the manufacture of plaster board and other building materials. The catalysis of anhydrite to give a quick-setting plaster without the furnacing which must be applied to gypsum was followed by the application of this principle to the manufacture of decorative flooring and wall compositions and light constructional building blocks for which a substantial demand developed. This work was carried out in conjunction with Imperial Chemical Industries Limited, which Company he joined in 1932 and from which he retired in 1944. While with I.C.I., he was on the Board of I.C.I. (Lime) Limited as Technical Director. From 1944 till his death on August 13th, 1947, following an operation, he was acting as adviser to a syndicate of French Industrialists called " *Placopatre* ", which was building and equipping factories for the manufacture of plaster board in France. In the

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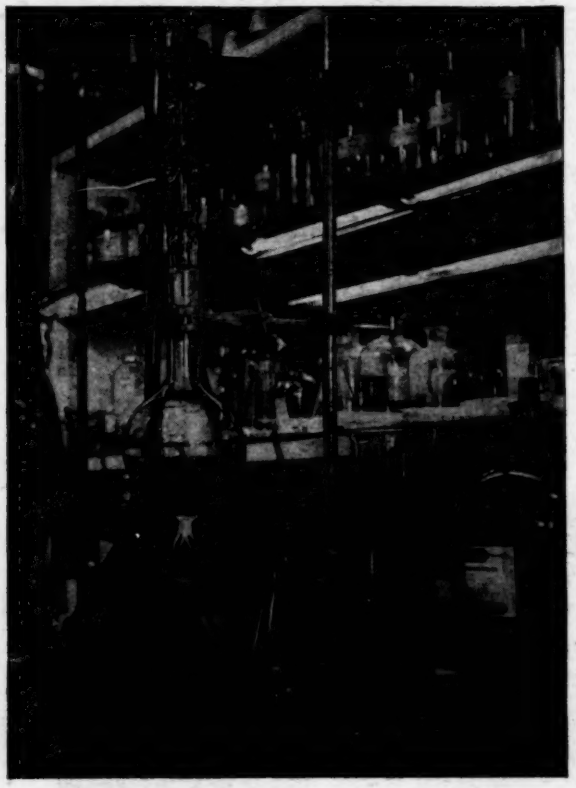

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